IAP20 Rec'd PCT/PTO 19 JUL 2006

IMIDAZOLE-BASED HMG-COA REDUCTASE INHIBITORS

FIELD OF THE INVENTION

The present invention relates to compounds and pharmaceutical compositions useful as hypocholesterolemic and hypolipidemic agents. More specifically, the present invention concerns certain potent inhibitors of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase ("HMG-CoA reductase"). The invention further relates to methods of using such compounds and compositions to treat subjects, including humans, suffering from hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, Alzheimer's Disease, BPH, diabetes and osteoporosis.

BACKGROUND OF THE INVENTION

High levels of blood cholesterol and blood lipids are conditions involved in the onset of atherosclerosis. The conversion of HMG-CoA to mevalonate is an early and rate-limiting step in the cholesterol biosynthetic pathway. This step is catalyzed by the enzyme HMG-CoA reductase. Statins inhibit HMG-CoA reductase from catalyzing this conversion. As such, statins are collectively potent lipid lowering agents. Thus, statins are the drugs of first choice for management of many lipid disorders. Representative statins include atorvastatin, lovastatin, pravastatin and simvastatin.

It is known that inhibitors of HMG-CoA reductase are effective in lowering the blood plasma level of low density lipoprotein cholesterol (LDL-C), in man. (cf. M.S. Brown and J.L. Goldstein, *New England Journal of Medicine*, 305, No. 9, 515-517 (1981)). It has been established that lowering LDL-C levels affords protection from coronary heart disease (cf. *Journal of the American Medical Association*, 251, No. 3, 351-374 (1984)). Further, it is known that certain derivatives of mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) and the corresponding ring-closed lactone form mevalonolactone, inhibit the biosynthesis of cholesterol (cf. F. M. Singer et al., *Proc. Soc. Exper. Biol. Med.*, 102: 370 (1959) and F.H. Hulcher, *Arch. Biochem. Biophys.*, 146: 422 (1971)).

U.S. Pat. Nos. 3,983,140; 4,049,495 and 4,137,322 disclose the fermentative production of a natural product, now called compactin, having an inhibitory effect on cholesterol biosynthesis. Compactin has been shown to have a complex structure which includes a mevalonolactone moiety (Brown et al., *J. Chem. Soc. Perkin* I (1976) 1165). U.S. Pat. No. 4,255,444 to Oka et al. discloses several synthetic derivatives of mevalonolactone having antilipidemic activity. U.S. Pat. Nos. 4,198,425 and 4,262,013 to Mitsue et al. disclose aralkyl derivatives of mevalonolactone which are useful in the treatment of hyperlipidemia.

Atorvastatin and pharmaceutically acceptable salts thereof are selective, competitive inhibitors of HMG-CoA reductase. As such, atorvastatin calcium is a potent lipid lowering compound and is thus useful as a hypolipidemic and/or hypocholesterolemic agent, as well as in the treatment of osteoporosis and Alzheimer's disease. A number of patents have issued disclosing atorvastatin. These include: United States Patent Numbers 4,681,893; 5,273,995 and 5,969,156, which are incorporated herein by reference.

All statins interfere, to varying degrees, with the conversion of HMG-CoA to the cholesterol precursor mevalonate by HMG-CoA reductase. These drugs share many features, but also exhibit differences in pharmacalogic attributes that may contribute to differences in clinical utility and effectiveness in modifying lipid risk factors for coronary heart disease. (Clin. Cardiol. Bol. 26 (Suppl. III), III-32-III-38 (2003)). Some of the desirable pharmocologic features with statin therapy include potent reversible inhibition of HMG-CoA reductase, the ability to produce large reductions in LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C), the ability to increase HDL cholesterol (HDL-C), tissue selectivity, optimal pharmacokinetics, availability of once a day dosing and a low potential for drug-drug interactions. Also desirable is the ability to lower circulating very-low-density-lipoprotein(VLDL) as well as the ability to lower triglyceride levels.

At the present time, the most potent statins display in vitro IC_{50} values, using purified human HMG-CoA reductase catalytic domain preparations, of between about 5.4 and about 8.0 nM. (*Am J. Cardiol* 2001;87(suppl):28B-32B; *Atheroscer Suppl.* 2002;2:33-37). Generally, the most potent LDL-C-lowering statins are also the most potent non-HDL-C-lowering statins. Thus, maximum inhibitory activity is desirable. With respect to HDL-C, the known statins

generally produce only modest increases in HDL-C. Therefore, the ability to effect greater increases in HDL-C would be advantageous as well.

With respect to tissue selectivity, differences among statins in relative lipophilicity or hydrophilicity may influence drug kinetics and tissue selectivity. Relatively hydrophilic drugs may exhibit reduced access to nonhepatic cells as a result of low passive diffusion and increased relative hepatic cell uptake through selective organic ion transport. In addition, the relative water solubility of a drug may reduce the need for extensive cytochrome P450 (CYP) enzyme metabolism. Many drugs, including the known statins, are metabolized by the CYP3A4 enzyme system. (*Arch Intern Med* 2000; 160:2273-2280; *J Am Pharm Assoc* 2000; 40:637-644). Thus, relative hydrophilicity is desirable with statin therapy.

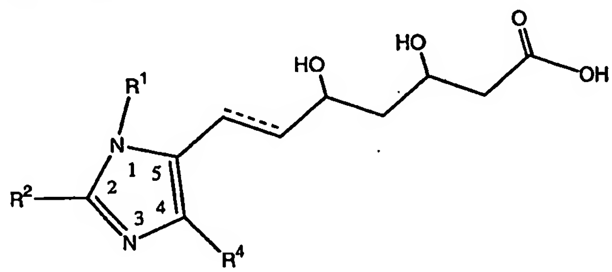
Two important pharmacokinetic variables for statins are bioavailability and elimination half-life. It would be advantageous to have a statin with limited systemic availability so as to minimize any potential risk of systemic adverse effects, while at the same time having enough systemic availability so that any pleiotropic effects can be observed in the vasculature with statin treatment. These pleiotropic effects include improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, reduction in blood plasma levels of certain markers of inflammation such as C-reactive protein, decreasing oxidative stress and reducing vascular inflammation. (*Arterioscler Thromb Vasc Biol* 2001; 21:1712-1719; *Heart Dis* 5(1):2-7, 2003). Further, it would be advantageous to have a statin with a long enough elimination half-life to maximize effectiveness for lowering LDL-C.

Finally, it would be advantageous to have a statin that is either not metabolized or minimally metabolized by the CYP 3A4 systems so as to minimize any potential risk of drug-drug interactions when statins are given in combination with other drugs.

Accordingly, it would be most beneficial to provide a statin having a combination of desirable properties including high potency in inhibiting HMG-CoA reductase, the ability to produce large reductions in LDL-C and non-high density lipoprotein cholesterol, the ability to increase HDL cholesterol, selectivity of effect or uptake in hepatic cells, optimal systemic bioavailability, prolonged elimination half-life, and absence or minimal metabolism via the CYP3A4 system.

SUMMARY OF THE INVENTION

This invention provides a novel series of imidazoles as HMG-CoA reductase inhibitors. Compounds of the invention are potent inhibitors of cholesterol biosynthesis. Accordingly, the compounds find utility as therapeutic agents to treat hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, Alzheimer's Disease, BPH, diabetes and osteoporosis. More specifically, the present invention provides a compound having a Formula I,



Formula I

or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein:

---------- is a bond or is absent;

R^1 is H; C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

R^2 is H; halogen; C_1-C_6 alkyl or C_3-C_8 cycloalkyl, optionally substituted; aryl, aralkyl, heteroaryl or heteroaralkyl, optionally substituted; $R^6R^7NS(O)_2$-; $R^8S(O)_n$-; -$(CH_2)_n$COR'; -$(CH_2)_n$NR^{6}R^7; -$(CH_2)_n$COOR'; or $R^6R^7NC(O)$-;

R^6 and R^7 are each independently H; aryl, aralkyl, heteroaryl or heteroaralkyl, optionally substituted with halogen, OR', $(CH_2)_n$COOR', $(CH_2)_n$CONR'R", $(CH_2)_n$SO$_2$R' or CN;

C_1-C_{10} alkyl, optionally substituted; $(CH_2)_n$COR'; $(CH_2)_n$COOR'; (CH_2)CONR'R" or $(CH_2)_n$SO$_2$R'; or

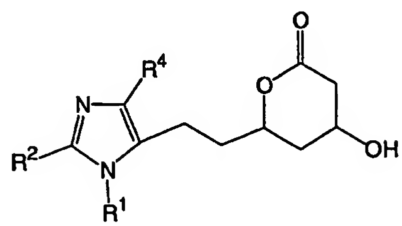
N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted;

R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, optionally substituted; H; halo; aryl or heteroaryl, optionally substituted;

R^8 is aryl, aralkyl, alkyl, heteroaryl or heteroaralkyl; optionally substituted,

R' and R" are each independently H; C_1-C_{12} alkyl, aryl or aralkyl; optionally substituted; and n is 0-2.

Further provided is a compound having a formula:



or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein:

R^1 is H; C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

R^2 is H; halogen; C_1-C_6 alkyl or C_3-C_8 cycloalkyl, optionally substituted; $R^6R^7NS(O)_2$-; $R^8S(O)_n$-; -$(CH_2)_nCOR'$; -NR^6R^7; -$(CH_2)_nCOOR'$; or $R^6R^7NC(O)$-;

R^6 and R^7 are each independently H; aryl, aralkyl, heteroaryl or heteroaralkyl, optionally substituted with halogen, OR', $(CH_2)_nCOOR'$, $(CH_2)_nCONR'R''$, $(CH_2)_nSO_2R'$ or CN;

C_1-C_{10} alkyl, optionally substituted; $(CH_2)_nCOR'$; $(CH_2)_nCOOR'$; $(CH_2)CONR'R''$; or $(CH_2)_nSO_2R'$; or

N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted;

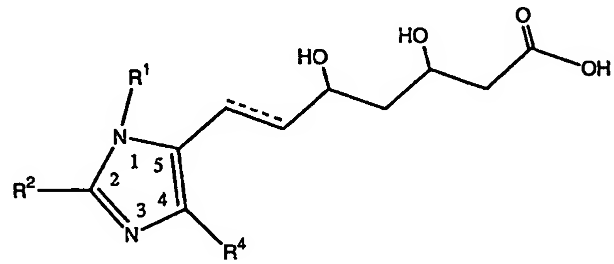
R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, optionally substituted; H; halo; aryl or heteroaryl, optionally substituted;

R^8 is aryl, aralkyl, alkyl, heteroaryl or heteroaralkyl; optionally substituted,

R' and R" are each independently H; C_1-C_{12} alkyl, aryl or aralkyl; optionally substituted; and n is 0-2.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a compound having a Formula I,



Formula I

or a pharmaceutically acceptable salt, ester, amide, stereoisomer or prodrug thereof, or a pharmaceutically acceptable salt of the prodrug, wherein:

---------- is a bond or is absent;

R^1 is H; C_1-C_6 alkyl or C_3-C_8 cycloalkyl;

R^2 is H; halogen; C_1-C_6 alkyl or C_3-C_8 cycloalkyl, optionally substituted; aryl, aralkyl, heteroaryl or heteroaralkyl, optionally substituted; $R^6R^7NS(O)_2$-; $R^8S(O)_n^-$; -$(CH_2)_n$COR'; -$(CH_2)_n$NR^{6}R^7; -$(CH_2)_n$COOR'; or $R^6R^7NC(O)$-;

R^6 and R^7 are each independently H; aryl, aralkyl, heteroaryl or heteroaralkyl, optionally substituted with halogen, OR', $(CH_2)_n$COOR', $(CH_2)_n$CONR'R", $(CH_2)_n$SO$_2$R' or CN;

C_1-C_{10} alkyl, optionally substituted; $(CH_2)_n$COR'; $(CH_2)_n$COOR'; (CH_2)CONR'R" or $(CH_2)_n$SO$_2$R'; or

N, R^6 and R^7 taken together form a 4-11 member ring optionally containing up to two heteroatoms selected from O, N and S, said ring being optionally substituted;

R^4 is C_1-C_6 alkyl or C_3-C_8 cycloalkyl, optionally substituted; H; halo; aryl or heteroaryl, optionally substituted;

R^8 is aryl, aralkyl, alkyl, heteroaryl or heteroaralkyl, optionally substituted;

R' and R" are each independently H; C_1-C_{12} alkyl, aryl or aralkyl, optionally substituted; and n is 0-2.

Further provided is the above-described compound wherein R^1 is C_{1-3} alkyl. Further provided is the compound wherein R^1 is isopropyl or cyclopropyl. Further provided is the compound wherein R^1 is ethyl.

Further provided is the above-described compound wherein R^2 is $R^6R^7NS(O)_2$- or $R^6R^7NC(O)$-. Further provided is the above-described compound or a pharmaceutically acceptable salt, solvate, or composition thereof wherein R^2 is -$(CH_2)_nNR^6R^7$.Further provided is the compound wherein R^6 and R^7 are each independently H; or aralkyl, optionally substituted.

Further provided is the compound wherein R^6 and R^7 are each independently H; phenyl, pyridinyl, phenyl-ethyl or benzyl, optionally substituted with halogen, CN, $(CH_2)_nCONR'R''$, $(CH_2)_nSO_2R'$, OR', or $(CH_2)_nCOOR'$; and R" and R' are each independently H or lower alkyl.

Further provided is the above-described compound wherein R^4 is H; lower alkyl, phenyl or heteroaryl; optionally substituted. Further provided is the compound wherein R^4 is phenyl substituted by one or more groups selected from halogen or $-CH_3$; or pyridinyl. Further provided is the compound wherein R^4 is 4-fluorophenyl, methylfluoro-phenyl or difluorophenyl.

Further provided is the above-described compound wherein R^6 and R^7 are each independently lower alkyl or phenyl; optionally substituted; or pyridinyl. Further provided is the compound wherein one of R^6 and R^7 is phenyl, optionally substituted, and the other one of R^6 and R^7 is methyl.

Further provided is the above-described compound wherein R^1 is isopropyl.

Further provided is a pharmaceutically acceptable salt of the above-described compound wherein the salt is a sodium salt or a calcium salt.

Further provided is a stereoisomer of the above-described compound comprising a (3R, 5R)- isomer or a pharmaceutically acceptable salt, ester or amide thereof. Further provided is the (3S, 5R)- isomer of the compound. Further provided is the (3S, 5S)- isomer of the compound. Further provided is the (3R, 5S)- isomer of the compound. Further provided is a racemic mixture comprising the compound.

Further provided is a pharmaceutically acceptable ester of the above-described compound wherein the ester is a methyl ester.

The present invention provides *inter alia* the following compounds: (3R,5R)-7-[2-Benzylcarbamoyl-5-(3,4-difluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5- dihydroxy-heptanoic acid; (3R,5R)-7-[2-benzylcarbamoyl-3-propyl-5-

(4-fluoro-phenyl)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-benzylcarbamoyl-3-isobutyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-benzylcarbamoyl-3-ethyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-benzylcarbamoyl-3-isopropyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenethylcarbamoyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-(4-fluoro-benzylcarbamoyl)-3-propyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-phenylcarbamoyl-3-propyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[2-(4-fluoro-benzylcarbamoyl)-5-(4-fluoro-3-methyl-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; (3R,5R)-7-(2-benzylcarbamoyl-3-isopropyl-5-pyridin-3-yl-3H-midazol-4-yl)-3,5-dihydroxy-heptanoic acid; (3R,5S)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazole-4-yl)-3,5-dihydroxy-hept-6-enoic acid; (3R,5R)-3,5-Dihydroxy-7-[3-isopropyl-5-phenyl-2-((R)-1-phenyl-ethylcarbamoyl)-3H-imidazol-4-yl]-heptanoic acid; (3R,5R)-3,5-dihydroxy-7-[3-isopropyl-5-phenyl-2-((S)-1-phenyl-ethylcarbamoyl)-3H-imidazol-4-yl]-heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-methanesulfonylamino-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-(methyl-phenylmethanesulfonyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonylamino-3H-midazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[2-benzenesulfonylamino-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[2-(benzenesulfonyl-methyl-amino)-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid sodium salt; 7-[2-(acetyl-methyl-amino)-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[2-acetylamino-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[2-(acetyl-benzyl-amino)-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid; 7-[2-(benzoyl-methyl-amino)-5-(4-fluoro-phenyl)-3-isopropyl-3H-

imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[2-benzoylamino-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylacetylamino-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-(methyl-phenylacetyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[2-(benzyl-methanesulfonyl-amino)-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-methylsulfamoyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[2-benzylsulfamoyl-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; 7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylsulfamoyl-3H-imidazol-4-yl]-3,5-dihydroxy- heptanoic acid; (3R,5R)-7-{5-(4-Fluoro-phenyl)-3-isopropyl-2-[(pyridin-3-ylmethyl)-carbamoyl]-3H-imidazol-4-yl}-3,5-dihydroxy- heptanoic acid; and pharmaceutically acceptable salts, amides and esters thereof.

Further provided is the use of the above-described compound for the manufacture of a medicament to treat a disease for which an HMG Co-A reductase inhibitor is indicated. Further provided is a combination of the above-described compound and another pharmaceutically active agent. Further provided is the combination wherein the other pharmaceutically active agent is a CTEP inhibitor, a PPAR-activator, an MTP/Apo B secretion inhibitor, a cholesterol absorption inhibitor, a cholesterol synthesis inhibitor, a fibrate, niacin, an ion-exchange resin, an antioxidant, an ACAT inhibitor, a bile sequestrant, an anti-hypertensive agent, or an acetylcholine esterase inhibitor.

Further provided is a pharmaceutical composition comprising the above-described compound or the above-described combination and a pharmaceutically acceptable carrier, diluent or vehicle. Further provided is the use of the above-described compound, combination or composition, for the manufacture of a medicament to treat atherosclerosis.

The following definitions are used, unless otherwise described herein. Halo is fluoro, chloro, bromo or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc. denote both straight and branched groups.

The term "alkyl" as used herein refers to a straight or branched hydrocarbon of from 1 to 11 carbon atoms and includes, for example, methyl,

ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like. The alkyl group can also be substituted with one or more of the substituents selected from lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, -NR'R" or –CONR'R" where R' and R" are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N, R' and R" taken together form a 4-7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C_1-C_6 alkyl).

The term "lower alkyl" as used herein refers to a subset of alkyl which means a straight or branched hydrocarbon radical having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, n-pentyl, n-hexyl, and the like. Optionally, lower alkyl is referred to as "C_1-C_6alkyl."

The term "haloalkyl" as used herein refers to a lower alkyl radical, as defined above, bearing at least one halogen substituent, for example, chloromethyl, fluoroethyl, trifluoromethyl, or 1,1,1-trifluoroethyl and the like. Haloalkyl can also include perfluoroalkyl wherein all hydrogens of a loweralkyl group are replaced with fluorine atoms.

The term "alkenyl" means a straight or branched unsaturated hydrocarbon radical from 2 to 12 carbon atoms and includes, for example, ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 1-pentenyl, 2-pentenyl, 3-methyl-3-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 3-heptenyl, l-octenyl, 1-nonenyl, 1-decenyl, 1-undecenyl, 1-dodecenyl, and the like.

The term "alkynyl" means a straight or branched hydrocarbon radical of 2 to 12 carbon atoms having at least one triple bond and includes, for example, 3-propynyl, 1-butynyl, 3-butynyl, 1-pentynyl, 3-pentynyl, 3-methyl-3-butynyl, 1-hexynyl, 3-hexynyl, 3-hexynyl, 3-heptynyl, l-octynyl, 1-nonynyl, 1-decynyl, 1-undecynyl, 1-dodecynyl, and the like.

The term "alkylene" as used herein refers to a divalent group derived from a straight or branched chain saturated hydrocarbon having from 1 to 10 carbon atoms by the removal of two hydrogen atoms, for example methylene, 1,2-ethylene, 1,1-ethylene, 1,3-propylene, 2,2- dimethylpropylene, and the like. The alkylene groups of this invention can be optionally substituted with one or more of

the substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, NR'R", or –CONR'R", where R' and R" are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N, R' and R" taken together form a 4-7 member ring. Useful alkylene groups have from 1 to 6 carbon atoms (C_1-C_6 alkylene).

The term "heteroatom" as used herein represents oxygen, nitrogen, or sulfur (O, N, or S) as well as sulfoxyl or sulfonyl (SO or SO_2) unless otherwise indicated.

The term "hydrocarbon chain" as used herein refers to a straight hydrocarbon of from 2 to 6 carbon atoms. The hydrocarbon chain is optionally substituted with one or more substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, NR'R" or –CONR'R", where R' and R" are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or joined together to form a 4 to 7 member ring; or N, R' and R" taken together form a 4-7 member ring.

The term "hydrocarbon-heteroatom chain" as used herein refers to a hydrocarbon chain wherein one or more carbon atoms are replaced with a heteroatom. The hydrocarbon-heteroatom chain is optionally substituted with one or more substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, NR'R" or –CONR'R", where R' and R" are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or joined together to form a 4 to 7 member ring; or N, R' and R" taken together form a 4-7 member ring.

The term "heteroalkylene" as used herein, refers to an alkylene radical as defined above that includes one or more heteroatoms such as oxygen, sulfur, or nitrogen (with valence completed by hydrogen or oxygen) in the carbon chain or terminating the carbon chain.

The terms "lower alkoxy" and "lower thioalkoxy" as used herein refers to O-alkyl or S-alkyl of from 1 to 6 carbon atoms as defined above for "lower alkyl."

The term "aryl" as used herein refers to an aromatic ring which is unsubstituted or optionally substituted by 1 to 4 substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1$-C_6 alkyl, -NR'R", $-S(O)_2$alkyl, $S(O)_2$aryl, $S(O)_2$NR'R", or –CONR'R", where R' and R" are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl or joined together to form a 4 to 7 member ring; or N, R' and R" taken together form a 4-7 member ring. Examples include, but are not limited to phenyl, biphenyl, naphthyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-chloro-3-methylphenyl, 2-chloro-4-methylphenyl, 2-chloro-5-methylphenyl, 3-chloro-2-methylphenyl, 3-chloro-4-methylphenyl, 4-chloro-2-methylphenyl, 4-chloro-3-methylphenyl, 5-chloro-2-methylphenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2,3-dimethylphenyl, 3,4-dimethylphenyl, or the like. Further, the term "aryl" means a cyclic or polycyclic aromatic ring having from 5 to 12 carbon atoms, and being unsubstituted or substituted with up to 4 of the substituent groups recited above for alkyl, alkenyl, and alkynyl.

The term aralkyl as used herein means aryl, as defined above, attached to an alkyl group as defined above.

The term "heteroaryl" means an aromatic ring containing one or more heteroatom. Further, the term "heteroaryl" means an aromatic mono-, bi-, or polycyclic ring incorporating one or more (i.e. 1-4) heteroatoms selected from N, O, and S. The heteroaryl is optionally substituted with one or more groups enumerated for aryl. Examples of heteroaryl include, but are not limited to thienyl, furanyl, pyrrolyl, pyridyl, pyrimidyl, imidazolyl, pyrazinyl, oxazolyl, thiazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, isoquinolinyl, and quinazolinyl, and the like. Examples further include 1-, 2-, 4-, or 5-imidazolyl, 1-, 3-, 4-, or 5-pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 1, 3-, or 5-triazolyl, 1-, 2-, or 3-tetrazolyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl. Specific examples of suitable bicyclic heteroaryl compounds include, but are not limited to indolizinyl, isoindolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzimidazolyl, quinolinyl,

isoquinolinyl, quinazolinyl, 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 1-, 2-, 3-, 5-, 6-, 7-, or 8-indolizinyl, 1-, 2-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzothienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 1-, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, and 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl.

The term heteroaralkyl, as used herein, means heteroaryl, as defined above, attached to an alkyl group is defined above.

The term "heterocycle" means a saturated mono- or polycyclic (i.e. bicyclic) ring incorporating one or more (i.e. 1-4) heteroatoms selected from N, O, and S. It is understood that a heterocycle is optionally substituted with one or more of the substituents selected from lower alkoxy, lower thioalkoxy, $-O(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, -NR'R" or–CONR'R" where R' and R" are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N, R' and R" taken together form a 4-7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C_1-C_6 alkyl). Examples of suitable monocyclic heterocycles include, but are not limited to piperidinyl, pyrrolidinyl, piperazinyl, azetidinyl, aziridinyl, morpholinyl, thietanyl, oxetaryl.

The term "cycloalkyl" means a saturated hydrocarbon ring. Further, the term "cycloalkyl" means a hydrocarbon ring containing from 3 to 12 carbon atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cycloctyl, decalinyl, norpinanyl, or adamantyl. The cycloalkyl ring may be unsubstituted or substituted by 1 to 3 substituents selected from one or more of the substituents selected from lower alkoxy, lower thioalkoxy, $-(CH_2)_{0-2}CF_3$, halogen, nitro, cyano, =O, =S, -OH, -SH, $-CF_3$, $-CO_2H$, $-CO_2C_1-C_6$ alkyl, -NR'R" or–CONR'R" where R' and R" are independently H, alkyl, cycloalkyl, akenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, or joined together to form a 4 to 7 member ring; or N, R' and R" taken together form a 4-7 member ring. Useful alkyl groups have from 1 to 6 carbon atoms (C_1-C_6 alkyl), wherein alkyl, aryl, and heteroaryl are as defined herein. Examples of substituted cycloalkyl groups include fluorocyclopropyl, 2-iodocyclobutyl, 2,3-dimethylcyclopentyl, 2,2-dimethoxycyclohexyl, and 3-phenylcyclopentyl.

The term "cycloalkenyl" means a cycloalkyl group having one or more carbon-carbon double bond. Example includes cyclobutene, cyclopentene, cyclohexene, cycloheptene, cyclobutadiene, cyclopentadiene, and the like.

The term "isomer" means "stereoisomer" and "geometric isomer" as defined below.

The term "stereoisomer" means compounds that possess one or more chiral centers and each center may exist in the R or S configuration. Stereoisomers includes all diastereomeric, enantiomeric and epimeric forms as well as racemates and mixtures thereof.

The term "geometric isomer" means compounds that may exist in cis, trans syn, anti, entgegen (E), and zusammen (Z) forms as well as mixtures thereof.

The symbol "=" means a double bond.

The symbol "$\cap$" means a bond to a group wherein a 4 to 8 membered ring is formed. Typically this symbol will appear in pairs.

When a bond to a substituent is shown to cross the bond connecting 2 atoms in a ring, then such substituent may be bonded to any atom in the ring, provided the atom will accept the substituent without violating its valency. When there appears to be several atoms of the substituent that may bond to the ring atom, then it is the first atom of the listed substituent that is attached to the ring.

When a bond from a substituent is shown to cross the bond connecting 2 atoms in a ring of the substituent, then such substituent may be bonded from any atom in the ring which is available.

When a bond is represented by a line such as "---" this is meant to represent that the bond may be absent or present provided that the resultant compound is stable and of satisfactory valency. If an asymmetric carbon is created by such a bond, a particular stereochemistry is not to be implied unless otherwise indicated.

As used herein, the following terms have the meanings given: RT or rt means room temperature. MP means melting point. MS means mass spectroscopy. TLC means thin layer chromatography. [S]at. means saturated. [C]onc. means concentrated. TBIA means *tert*- Butylisopropylidene amine. DCM means dichloromethane, which is used interchangeably with methylene chloride. NBS means *N*-Bromosuccinimide. "h" means hour. "v/v" means volume ratio or

"volume per volume". R_f means retention factor. Tf_2O means "triflic anhydride" or $C(F)_3S(O)_2OS(O)_2C(F)_3$ or$(CF_3SO_2)O$. Ac_2O means acetic anhydride. "[T]rifluorotol." Or "TFT" means trifluorotoluene. "DMF" means dimethylformamide. "DCE" means dichloroethane. "Bu" means butyl. "Me" means methyl. "Et" means ethyl. "DBU" means 1,8-Diazabicyclo-[5.4.0]undec-7-ene. "TBS" means "TBDMS" or tert-Butyldimethylsilyl. "DMSO" means dimethyl sulfoxide. "TBAF" means tetrabutylammonium fluoride. THF means tetrahydrofuran. [N]-BuLi or BuLi means n-butyl lithium. TFA means trifluoroacetic acid. i-Pr means isopropyl. [M]in. means minutes. ml or mL means milliliter. "M" or "m" means molar.

The term "patient" means all mammals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, pigs, and rabbits.

A "therapeutically effective amount" is an amount of a compound of the present invention that when administered to a patient ameliorates a symptom of hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atheroscelerois, BPH, Alzheimer's Disease, diabetes or osteoporosis.

The term "a pharmaceutically acceptable salt, ester, amide, or prodrug" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "a pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared in situ during the final isolation and purification of the compounds or by separately reacting the purified compound in its free form with a suitable organic or inorganic acid or base and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like.

Pharmaceutically acceptable salts may also include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, and the like, as well as non-toxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, Berge S.M., et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19, which is incorporated herein by reference.) The free base form may be regenerated by contacting the salt form with a base. While the free base may differ from the salt form in terms of physical properties, such as solubility, the salts are equivalent to their respective free bases for the purposes of the present invention.

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines, the amine may also be in the form of a 5- or 6-membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

"Prodrugs" are intended to include any covalently bonded carrier which releases the active parent drug according to Formula I *in vivo*. Further, the term "prodrug" refers to compounds that are transformed in vivo to yield the parent compound of the above formulae, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are hereby incorporated by

reference. Examples of prodrugs include acetates, formates, benzoate derivatives of alcohols, and amines present in compounds of Formula I.

In some situations, compounds may exist as tautomers. All tautomers are included within Formula I and are provided by this invention.

Certain compounds of the present invention can exist in unsolvated form as well as solvated form including hydrated form. In general, the solvated form including hydrated form is equivalent to unsolvated form and is intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Stereoisomers may be obtained, if desired, by methods known in the art as, for example, the separation of stereoisomers by chiral chromatographic columns and by chiral synthesis. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all cis, trans, syn, anti, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

The compounds of the present invention are suitable to be administered to a patient for the treatment, control, or prevention of, hypercholesteremia, hyperlipidemia, atherosclerosis, hypertriglyceridemia, BPH, Alzheimer's Disease, diabetes and osteoprosis. The terms "treatment", "treating", "controlling", "preventing" and the like, refers to reversing, alleviating, or inhibiting the progress of the disease or condition to which such term applies, or one or more symptoms of such disease or condition. As used herein, these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition, including reducing the severity of a disease or condition or symptoms associated therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound of the invention to a subject that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence of a disease or condition or of symptoms associated therewith. Accordingly, the compounds of the present invention can be administered to a patient alone or as

part of a composition that contains other components such as excipients, diluents, and carriers, all of which are well-known in the art. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly, or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid; (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia; (c) humectants, as for example, glycerol; (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate; (e) solution retarders, as for

example paraffin; (f) absorption accelerators, as for example, quaternary ammonium compounds; (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate; (h) adsorbents, as for example, kaolin and bentonite; and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol

and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalmic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present invention can be administered to a patient at dosage levels in the range of about 0.1 to about 2,000 mg per day. For a normal human adult having a body weight of about 70 kilograms, a dosage in the range of about 0.01 to about 100 mg per kilogram of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

Combination Aspect of the Invention

The compounds of this invention may be used, either alone or in combination with the other pharmaceutical agents described herein, in the treatment of the following diseases/conditions: dyslipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, peripheral vascular disease, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, diabetes and vascular complications of diabetes, obesity, unstable angina pectoris,

Alzheimer's Disease, BPH, osteoporosis, cerebrovascular disease, coronary artery disease, ventricular dysfunction, cardiac arrhythmia, pulmonary vascular disease, renal-vascular disease, renal disease, vascular hemostatic disease, autoimmune disorders, pulmonary disease, sexual dysfunction, cognitive dysfunction, cancer, organ transplant rejection, psoriasis, endometriosis, and macular degeneration.

The compounds of this invention may also be used in conjunction with other pharmaceutical agents (e.g., HDL-cholesterol raising agents, triglyceride lowering agents) for the treatment of the disease/conditions described herein. A combination aspect of this invention includes a pharmaceutical composition comprising a compound of this invention or its pharmaceutically acceptable salt and at least one other compound. For example, the compounds of this invention may be used in combination with cholesterol absorption inhibitors, MTP/Apo B secretion inhibitors, or other cholesterol modulating agents such as fibrates, niacin, ion-exchange resins, antioxidants, ACAT inhibitors, PPAR-activators, CETP inhibitors or bile acid sequestrants. In combination therapy treatment, both the compounds of this invention and the other drug therapies are administered to mammals by conventional methods. The following discussion more specifically describes the various combination aspects of this invention.

Any cholesterol absorption inhibitor can be used in a combination aspect of this invention. The term cholesterol absorption inhibition refers to the ability of a compound to prevent cholesterol contained within the lumen of the intestine from entering into the intestinal cells and/or passing from within the intestinal cells into the blood stream. Such cholesterol absorption inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Lipid Res. (1993) 34: 377-395). Cholesterol absorption inhibitors are known to those skilled in the art and are described, for example, in PCT WO 94/00480. An example of a recently approved cholesterol absorption inhibitor is ZETIA™.

Any cholesterol ester transfer protein ("CETP") inhibitor may be used in a combination aspect of this invention. The term CETP inhibitor refers to compounds that inhibit the transfer of cholesteryl ester and triglyceride between lipoprotein particles, including high density lipoproteins (HDL), low density lipoproteins (LDL), very low density lipoproteins (VLDL), and chylomicrons. The net result of CETP activity is a lowering of HDL cholesterol and an increase

in LDL cholesterol, such net effect therefore being pro-atherogenic. Thus, the effect of a CETP inhibitor on lipoprotein profile is believed to be anti-atherogenic. Such inhibition is readily determined by those skilled in the art by determining the amount of agent required to alter plasma lipid levels, for example HDL cholesterol levels, LDL cholesterol levels, VLDL cholesterol levels or triglycerides, in the plasma of certain mammals, (e.g., Crook et al. Arteriosclerosis 10, 625, 1990; U.S. Pat. No. 6,140,343). A variety of these compounds are described and referenced below, however other CETP inhibitors will be known to those skilled in the art. For example, U.S. Patent Nos. 6,197,786, 6,723,752 and 6,723,753 (the disclosures of each of which is incorporated herein by reference) disclose cholesteryl ester transfer protein inhibitors, pharmaceutical compositions containing such inhibitors and the use of such inhibitors to elevate certain plasma lipid levels, including high density lipoprotein-cholesterol and to lower certain other plasma lipid levels, such as LDL-cholesterol and triglycerides and accordingly to treat diseases which are exacerbated by low levels of HDL cholesterol and/or high levels of LDL-cholesterol and triglycerides, such as atherosclerosis and cardiovascular diseases in some mammals, including humans. Examples of useful CETP inhibitors include the following compounds: [2R, 4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydroxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester, which is also known as Torcetrapib™, and 3-{[3-(4-Chloro-3-ethyl-phenoxy)-phenyl]-[3-(1,1,2,2-tetrafluoro-ethoxy)-benzyl]-amino}-1,1,1-trifluoro-propan-2-ol. Many of the CETP inhibitors of this invention are poorly soluble and a dosage form that increases solubility facilitates the administration of such compounds. One such dosage form is a dosage form comprising (1) a solid amorphous dispersion comprising a cholesteryl ester transfer protein (CETP) inhibitor and an acidic concentration-enhancing polymer; and (2) an acid-sensitive HMG-CoA reductase inhibitor. This dosage form is more fully described in USSN 10/739,567 and entitled "Dosage Forms Comprising a CETP Inhibitor and an HMG-CoA Reductase Inhibitor", the specification of which is incorporated herein by reference.

Any compound that activates or otherwise interacts with a human peroxisome proliferator activated receptor ("PPAR") may be used in a combination aspect of this invention. Three mammalian peroxisome proliferator-activated receptors have been isolated and termed PPAR-alpha, PPAR-gamma, and PPAR-beta (also known as NUC1 or PPAR-delta). These PPARs regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements. These elements have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs play a pivotal role in the adipogenic signaling cascade and lipid homeostasis. PPAR-gamma receptors are associated with regulation of insulin sensitivity and blood glucose levels. PPAR-α activators are associated with lowering plasma triglycerides and LDL cholesterol. PPAR-β activators have been reported to both increase HDL-C levels and to decrease LDL-C levels. Thus, activation of PPAR-β alone, or in combination with the simultaneous activation of PPAR-α and/or PPAR-gamma may be desirable in formulating a treatment for dyslipidemia in which HDL is increased and LDL lowered. PPAR-activation is readily determined by those skilled in the art by the standard assays (e.g. US 2003/0225158 and US 2004/0157885). A variety of these compounds are described and referenced below, however other PPAR-activator compounds will be known to those skilled in the art. The following patents and published patent applications, the disclosure of each of which is incorporated herein by reference, provides a sampling. US 2003/0225158 discloses compounds that alter PPAR activity and methods of using them as therapeutic agents for treating or preventing dyslipidemia, hypercholesterolemia, obesity, hyperglycemia, atherosclerosis and hypertriglyceridemia. U.S. Pat. No. 6,710,063 discloses selective activators of PPAR delta. US 2003/0171377 discloses certain PPAR-activator compounds that are useful as anti-diabetic agents. US 2004/0157885 relates to PPAR agonists, in particular, certain PPARα agonists, pharmaceutical compositions containing such agonists and the use of such agonists to treat atherosclerosis, hypercholesterolemia, hypertriglyceridemia, diabetes, obesity, osteoporosis and Syndrome X or metabolic syndrome.

Examples of useful PPAR-activator compounds include the following compounds: [5-Methoxy-2-methly-4-(4'-trifluoromethly-biphenyl-4ylmethylsulfanyl)-phenoxy]-acetic acid; [5-Methoxy-2-methyl-4-(3'-trifloromethly-biphenyl-4-ylmethylsulfanyl)-phenoxy]-acetic acid; [4-(4'Fluoro-biphenyl-4-ylmethylsulfanyl)-5-methoxy-2methyl-phenoxy]-acetic acid; {5-Methoxy-2methyl-4-[4-(4-trifluoromethyl-benzyloxy)-benzylsulfanyl]-phenoxy}-acetic acid; {{5-Methoxy-2-methyl-4-[4-(5-trifluoromethyl-pryidin-2-yl)-benzylsulfanyl]-phenoxy}-acetic acid; (4-{4-[2-(3-Fluoro-phenyl)-vinyl]-benzylsulfanyl}-5-methoxy-2-methyl-phenoxy)-acetic acid; [5-Methoxy-2-methyl-4-(3-methyl-4'-trifluoromethyl-biphenyl-4-ylmethylsulfanyl)-phenoxy]-acetic acid; [5-Methoxy-2-methyl-4-(4'-trifluoromethyl-biphenyl-3-ylmethylsulfanyl)-phenoxy]- acetic acid; {5-Methoxy-2-methyl-4-[2-(4-trifluoromethyl-benzyloxy)-benzylsulfanyl]-phenoxy}acetic acid; 3-{5-[2-(-5-Methyl-2 phenyl-oxazol-4-yl-ethoxy] –indol- 1-yl} –propionic acid; 3-{4[2-(5-methyl-2- phenyl-1,3-oxazol-4-yl)ethoxy- 1H-indazol-1yl}propanoic acid; 2-Methyl-2-{3-[({2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]carbonyl}amino)methyl]phenoxy}propionic acid; 1-{3'-[2-5-Methyl-2-phenyl-1,3-oxazol-4-y]-1,1' –biphenyl-3-yl}oxy)cyclobutanecarboxylic acid; 3-[3-(1-Carboxy-1-methyl-ethoxy)-phenyl]-piperidine-1-carboxylic acid 3-trifluoromethyl-benzyl ester; 2-{2-methyl-4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid; 2-{2-methyl-4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-oxazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid; methyl 2-{4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sul fanyl]phenoxy}acetate; 2-{4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid; (E)-3-[2-methyl-4-({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methoxy)phenyl]-2-propenoic acid; 2-{3-chloro-4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenyl}acetic acid; 2-{2-methyl-4-[({4-methyl-2-[3-fluoro-4-(trifluoromethyl)phenyl]-1,3-thiazo l-5-

yl}methyl)sulfanyl]phenoxy}acetic acid; and pharmaceutically acceptable salts thereof.

Any MTP/Apo B secretion (microsomal triglyceride transfer protein and/or apolipoprotein B secretion) inhibitor can be used in the combination aspect of the present invention. The term MTP/Apo B secretion inhibitor refers to compounds, which inhibit the secretion of triglycerides, cholesteryl ester and phospholipids. Such inhibition is readily determined by those skilled in the art according to standard assays (e.g., Wetterau, J. R. 1992; Science 258:999). A variety of these compounds are known to those skilled in the art, including imputapride (Bayer) and additional compounds such as those disclosed in WO 96/40640 and WO 98/23593.

Any ACAT inhibitor can serve in the combination therapy aspect of the present invention. The term ACAT inhibitor refers to compounds that inhibit the intracellular esterification of dietary cholesterol by the enzyme acyl CoA: cholesterol acyltransferase. Such inhibition may be determined readily by one of skill in the art according to standard assays, such as the method of Heider et al. described in Journal of Lipid Research. 24:1127 (1983). A variety of these compounds are known to those skilled in the art, for example, U.S. Pat. No. 5,510,379 discloses certain carboxysulfonates, while WO 96/26948 and WO 96/10559 both disclose urea derivatives having ACAT inhibitory activity. Examples of ACAT inhibitors include compounds such as Avasimibe (Pfizer), CS-505 (Sankyo) and Eflucimibe (Eli Lilly and Pierre Fabre).

A lipase inhibitor can serve in the combination therapy aspect of the present invention. A lipase inhibitor is a compound that inhibits the metabolic cleavage of dietary triglycerides into free fatty acids and monoglycerides. Under normal physiological conditions, lipolysis occurs via a two-step process that involves acylation of an activated serine moiety of the lipase enzyme. This leads to the production of a fatty acid-lipase hemiacetal intermediate, which is then cleaved to release a diglyceride. Following further deacylation, the lipase-fatty acid intermediate is cleaved, resulting in free lipase, a monoglyceride and a fatty acid. The resultant free fatty acids and monoglycerides are incorporated into bile acid-phospholipid micelles, which are subsequently absorbed at the level of the brush border of the small intestine. The micelles eventually enter the peripheral

circulation as chylomicrons. Such lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

Pancreatic lipase mediates the metabolic cleavage of fatty acids from triglycerides at the 1- and 3-carbon positions. The primary site of the metabolism of ingested fats is in the duodenum and proximal jejunum by pancreatic lipase, which is usually secreted in vast excess of the amounts necessary for the breakdown of fats in the upper small intestine. Because pancreatic lipase is the primary enzyme required for the absorption of dietary triglycerides, inhibitors have utility in the treatment of obesity and the other related conditions. Such pancreatic lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

Gastric lipase is an immunologically distinct lipase that is responsible for approximately 10 to 40% of the digestion of dietary fats. Gastric lipase is secreted in response to mechanical stimulation, ingestion of food, the presence of a fatty meal or by sympathetic agents. Gastric lipolysis of ingested fats is of physiological importance in the provision of fatty acids needed to trigger pancreatic lipase activity in the intestine and is also of importance for fat absorption in a variety of physiological and pathological conditions associated with pancreatic insufficiency. See, for example, C. K. Abrams, et al., Gastroenterology, 92,125 (1987). Such gastric lipase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. 286: 190-231).

A variety of gastric and/or pancreatic lipase inhibitors are known to one of ordinary skill in the art. Preferred lipase inhibitors are those inhibitors that are selected from the group consisting of lipstatin, tetrahydrolipstatin (orlistat), valilactone, esterastin, ebelactone A, and ebelactone B. The compound tetrahydrolipstatin is especially preferred. The lipase inhibitor, N-3-trifluoromethylphenyl-N'-- 3-chloro-4'-trifluoromethylphenylurea, and the various urea derivatives related thereto, are disclosed in U.S. Pat. No. 4,405,644. The lipase inhibitor, esteracin, is disclosed in U.S. Pat. Nos. 4,189,438 and 4,242,453. The lipase inhibitor, cyclo-O,O'-[(1,6-hexanediyl)-bis-(iminoc- arbonyl)]dioxime,

and the various bis(iminocarbonyl)dioximes related thereto may be prepared as described in Petersen et al., Liebig's Annalen, 562, 205-229 (1949).

A variety of pancreatic lipase inhibitors are described herein below. The pancreatic lipase inhibitors lipstatin, (2S,3S,5S,7Z,10Z)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydro- xy-7,10-hexadecanoic acid lactone, and tetrahydrolipstatin (orlistat), (2S,3S,5S)-5-[(S)-2-formamido-4-methyl-valeryloxy]-2-hexyl-3-hydroxy-hexa- decanoic 1,3 acid lactone, and the variously substituted N-formylleucine derivatives and stereoisomers thereof, are disclosed in U.S. Pat. No. 4,598,089. For example, tetrahydrolipstatin is prepared as described in, e.g., U.S. Pat. Nos. 5,274,143; 5,420,305; 5,540,917; and 5,643,874. The pancreatic lipase inhibitor, FL-386, 1-[4-(2-methylpropyl)cyclohexyl]-2-[-(phenylsulfonyl)oxy]-ethanone, and the variously substituted sulfonate derivatives related thereto, are disclosed in U.S. Pat. No. 4,452,813. The pancreatic lipase inhibitor, WAY-121898, 4-phenoxyphenyl-4-methylpipe- ridin-1-yl-carboxylate, and the various carbamate esters and pharmaceutically acceptable salts related thereto, are disclosed in U.S. Pat. Nos. 5,512,565; 5,391,571 and 5,602,151. The pancreatic lipase inhibitor, valilactone, and a process for the preparation thereof by the microbial cultivation of Actinomycetes strain MG147-CF2, are disclosed in Kitahara, et al., J. Antibiotics, 40 (11), 1647-1650 (1987). The pancreatic lipase inhibitors, ebelactone A and ebelactone B, and a process for the preparation thereof by the microbial cultivation of Actinomycetes strain MG7-G1, are disclosed in Umezawa, et al., J. Antibiotics, 33, 1594-1596 (1980). The use of ebelactones A and B in the suppression of monoglyceride formation is disclosed in Japanese Kokai 08-143457, published Jun. 4, 1996.

Other compounds that are marketed for hyperlipidemia, including hypercholesterolemia and which are intended to help prevent or treat atherosclerosis include bile acid sequestrants, such as Welchol®, Colestid®, LoCholest®, Questran® and fibric acid derivatives, such as Atromid®, Lopid® and Tricor®.

Compunds of the present invention can be used with anti-diabetic compounds. Diabetes can be treated by administering to a patient having diabetes (especially Type II), insulin resistance, impaired glucose tolerance, or the like, or any of the diabetic complications such as neuropathy, nephropathy, retinopathy or

cataracts, a therapeutically effective amount of a Formula I compound in combination with other agents (e.g., insulin) that can be used to treat diabetes. This includes the classes of anti-diabetic agents (and specific agents) described herein.

Any glycogen phosphorylase inhibitor can be used in combination with a Formula I compound of the present invention. The term glycogen phosphorylase inhibitor refers to compounds that inhibit the bioconversion of glycogen to glucose-1-phosphate which is catalyzed by the enzyme glycogen phosphorylase. Such glycogen phosphorylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., J. Med. Chem. 41 (1998) 2934-2938). A variety of glycogen phosphorylase inhibitors are known to those skilled in the art including those described in WO 96/39384 and WO 96/39385. Any aldose reductase inhibitor can be used in combination with a Formula I compound of the present invention. The term aldose reductase inhibitor refers to compounds that inhibit the bioconversion of glucose to sorbitol, which is catalyzed by the enzyme aldose reductase. Aldose reductase inhibition is readily determined by those skilled in the art according to standard assays (e.g., J. Malone, Diabetes, 29:861-864 (1980). "Red Cell Sorbitol, an Indicator of Diabetic Control"). A variety of aldose reductase inhibitors are known to those skilled in the art.

Any sorbitol dehydrogenase inhibitor can be used in combination with a Formula I compound of the present invention. The term sorbitol dehydrogenase inhibitor refers to compounds that inhibit the bioconversion of sorbitol to fructose which is catalyzed by the enzyme sorbitol dehydrogenase. Such sorbitol dehydrogenase inhibitor activity is readily determined by those skilled in the art according to standard assays (e.g., Analyt. Biochem (2000) 280: 329-331). A variety of sorbitol dehydrogenase inhibitors are known, for example, U.S. Pat. Nos. 5,728,704 and 5,866,578 disclose compounds and a method for treating or preventing diabetic complications by inhibiting the enzyme sorbitol dehydrogenase.

Any glucosidase inhibitor can be used in combination with a Formula I compound of the present invention. A glucosidase inhibitor inhibits the enzymatic hydrolysis of complex carbohydrates by glycoside hydrolases, for example

amylase or maltase, into bioavailable simple sugars, for example, glucose. The rapid metabolic action of glucosidases, particularly following the intake of high levels of carbohydrates, results in a state of alimentary hyperglycemia which, in adipose or diabetic subjects, leads to enhanced secretion of insulin, increased fat synthesis and a reduction in fat degradation. Following such hyperglycemias, hypoglycemia frequently occurs, due to the augmented levels of insulin present. Additionally, it is known chyme remaining in the stomach promotes the production of gastric juice, which initiates or favors the development of gastritis or duodenal ulcers. Accordingly, glucosidase inhibitors are known to have utility in accelerating the passage of carbohydrates through the stomach and inhibiting the absorption of glucose from the intestine. Furthermore, the conversion of carbohydrates into lipids of the fatty tissue and the subsequent incorporation of alimentary fat into fatty tissue deposits is accordingly reduced or delayed, with the concomitant benefit of reducing or preventing the deleterious abnormalities resulting therefrom. Such glucosidase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Biochemistry (1969) 8: 4214).

A generally preferred glucosidase inhibitor includes an amylase inhibitor. An amylase inhibitor is a glucosidase inhibitor that inhibits the enzymatic degradation of starch or glycogen into maltose. Such amylase inhibition activity is readily determined by those skilled in the art according to standard assays (e.g., Methods Enzymol. (1955) 1: 149). The inhibition of such enzymatic degradation is beneficial in reducing amounts of bioavailable sugars, including glucose and maltose, and the concomitant deleterious conditions resulting therefrom.

A variety of glucosidase inhibitors are known to one of ordinary skill in the art and examples are provided below. Preferred glucosidase inhibitors are those inhibitors that are selected from the group consisting of acarbose, adiposine, voglibose, miglitol, emiglitate, camiglibose, tendamistate, trestatin, pradimicin-Q and salbostatin. The glucosidase inhibitor, acarbose, and the various amino sugar derivatives related thereto are disclosed in U.S. Pat. Nos. 4,062,950 and 4,174,439 respectively. The glucosidase inhibitor, adiposine, is disclosed in U.S. Pat. No. 4,254,256. The glucosidase inhibitor, voglibose, 3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethy- 1)-D-epi-inositol, and the

various N-substituted pseudo-aminosugars related thereto, are disclosed in U.S. Pat. No. 4,701,559. The glucosidase inhibitor, miglitol, (2R,3R,4R,5S)-1-(2-hydroxyethyl)-2-(hydr- oxymethyl)-3,4,5-piperidinetriol, and the various 3,4,5-trihydroxypiperidines related thereto, are disclosed in U.S. Pat. No. 4,639,436. The glucosidase inhibitor, emiglitate, ethyl p-[2-[(2R,3R,4R,5S)-3,4,5-trihyd-roxy-2-(hydroxymethyl)piperidino]ethoxy]-benzoate, the various derivatives related thereto and pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Pat. No. 5,192,772. The glucosidase inhibitor, MDL-25637, 2,6-dideoxy-7-O-.beta.-D-glucopyrano-syl-2,6-imino-- D-glycero-L-gluco-heptitol, the various homodisaccharides related thereto and the pharmaceutically acceptable acid addition salts thereof, are disclosed in U.S. Pat. No. 4,634,765. The glucosidase inhibitor, camiglibose, methyl 6-deoxy-6-[(2R,3R,4R,5S)-3,4,5-trihydroxy-2-(hydroxym- ethyl)piperidino]-.alpha.-D-glucopyranoside sesquihydrate, the deoxy-nojirimycin derivatives related thereto, the various pharmaceutically acceptable salts thereof and synthetic methods for the preparation thereof, are disclosed in U.S. Pat. Nos. 5,157,116 and 5,504,078. The glycosidase inhibitor, salbostatin and the various pseudosaccharides related thereto, are disclosed in U.S. Pat. No. 5,091,524.

A variety of amylase inhibitors are known to one of ordinary skill in the art. The amylase inhibitor, tendamistat and the various cyclic peptides related thereto, are disclosed in U.S. Pat. No. 4,451,455. The amylase inhibitor AI-3688 and the various cyclic polypeptides related thereto are disclosed in U.S. Pat. No. 4,623,714. The amylase inhibitor, trestatin, consisting of a mixture of trestatin A, trestatin B and trestatin C and the various trehalose-containing aminosugars related thereto are disclosed in U.S. Pat. No. 4,273,765.

Additional anti-diabetic compounds, which can be used in combination with a Formula I compound of the present invention, includes, for example, the following: biguanides (e.g., metformin), insulin secretagogues (e.g., sulfonylureas and glinides), glitazones, non-glitazone PPAR.gamma. agonists, PPAR.beta. agonists, inhibitors of DPP-IV, inhibitors of PDE5, inhibitors of GSK-3, glucagon antagonists, inhibitors of f-1,6-BPase (Metabasis/Sankyo), GLP-1/analogs (AC 2993, also known as exendin-4), insulin and insulin mimetics (Merck natural

products). Other examples would include PKC-.beta. inhibitors and AGE breakers.

Compounds of the present invention can be used in combination with anti-obesity agents. Any anti-obesity agent can be used in such combinations and examples are provided herein. Such anti-obesity activity is readily determined by those skilled in the art according to standard assays known in the art. Suitable anti-obesity agents include phenylpropanolamine, ephedrine, pseudoephedrine, phentermine, .beta..sub.3 adrenergic receptor agonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, MCR-4 agonists, cholecystokinin-A (CCK-A) agonists, monoamine reuptake inhibitors (e.g., sibutramine), sympathomimetic agents, serotoninergic agents, cannabinoid receptor antagonists (e.g., rimonabant (SR-141,716A)), dopamine agonists (e.g., bromocriptine), melanocyte-stimulating hormone receptor analogs, 5HT2c agonists, melanin concentrating hormone antagonists, leptin (the OB protein), leptin analogs, leptin receptor agonists, galanin antagonists, lipase inhibitors (e.g., tetrahydrolipstatin, i.e. orlistat), bombesin agonists, anorectic agents (e.g., a bombesin agonist), Neuropeptide-Y antagonists, thyroxine, thyromimetic agents, dehydroepiandrosterones or analogs thereof, glucocorticoid receptor agonists or antagonists, orexin receptor antagonists, urocortin binding protein antagonists, glucagon-like peptide-1 receptor agonists, ciliary neurotrophic factors (e.g., Axokine.TM.), human agouti-related proteins (AGRP), ghrelin receptor antagonists, histamine 3 receptor antagonists or inverse agonists, neuromedin U receptor agonists, and the like.

Any thyromimetic can be used in combination with compounds of the present invention. Such thyromimetic activity is readily determined by those skilled in the art according to standard assays (e.g., Atherosclerosis (1996) 126: 53-63). A variety of thyromimetic agents are known to those skilled in the art, for example those disclosed in U.S. Pat. Nos. 4,766,121; 4,826,876; 4,910,305; 5,061,798; 5,284,971; 5,401,772; 5,654,468; and 5,569,674. Other antiobesity agents include sibutramine which can be prepared as described in U.S. Pat. No. 4,929,629. and bromocriptine which can be prepared as described in U.S. Pat. Nos. 3,752,814 and 3,752,888.

Osteoporosis is a systemic skeletal disease, characterized by low bone mass and deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. In the U.S., the condition affects more than 25 million people and causes more than 1.3 million fractures each year, including 500,000 spine, 250,000 hip and 240,000 wrist fractures annually. Hip fractures are the most serious consequence of osteoporosis, with 5-20% of patients dying within one year, and over 50% of survivors being incapacitated. The elderly are at greatest risk of osteoporosis, and the problem is therefore predicted to increase significantly with the aging of the population. Worldwide fracture incidence is forecasted to increase three-fold over the next 60 years, and one study has estimated that there will be 4.5 million hip fractures worldwide in 2050. Women are at greater risk of osteoporosis than men. Women experience a sharp acceleration of bone loss during the five years following menopause. Other factors that increase the risk include smoking, alcohol abuse, a sedentary lifestyle and low calcium intake.

Those skilled in the art will recognize that anti-resorptive agents (for example progestins, polyphosphonates, bisphosphonate(s), estrogen agonists/antagonists, estrogen, estrogen/progestin combinations, Premarin.RTM., estrone, estriol or 17.alpha.- or 17.beta.-ethynyl estradiol) may be used in conjunction with the compounds of Formula I of the present invention. Exemplary progestins are available from commercial sources and include: algestone acetophenide, altrenogest, amadinone acetate, anagestone acetate, chlormadinone acetate, cingestol, clogestone acetate, clomegestone acetate, delmadinone acetate, desogestrel, dimethisterone, dydrogesterone, ethynerone, ethynodiol diacetate, etonogestrel, flurogestone acetate, gestaclone, gestodene, gestonorone caproate, gestrinone, haloprogesterone, hydroxyprogesterone caproate, levonorgestrel, lynestrenol, medrogestone, medroxyprogesterone acetate, melengestrol acetate, methynodiol diacetate, norethindrone, norethindrone acetate, norethynodrel, norgestimate, norgestomet, norgestrel, oxogestone phenpropionate, progesterone, quingestanol acetate, quingestrone, and tigestol. Preferred progestins are medroxyprogestrone, norethindrone and norethynodrel. Exemplary bone resorption inhibiting polyphosphonates include polyphosphonates of the type disclosed in U.S. Pat. No. 3,683,080, the disclosure

of which is incorporated herein by reference. Preferred polyphosphonates are geminal diphosphonates (also referred to as bis-phosphonates). Tiludronate disodium is an especially preferred polyphosphonate. Ibandronic acid is an especially preferred polyphosphonate. Alendronate and resindronate are especially preferred polyphosphonates. Zoledronic acid is an especially preferred polyphosphonate. Other preferred polyphosphonates are 6-amino-1-hydroxy-hexylidene-bisphosphonic acid and 1-hydroxy-3(methylpentylamino)-propylidene-bisphosphonic acid. The polyphosphonates may be administered in the form of the acid, or of a soluble alkali metal salt or alkaline earth metal salt. Hydrolyzable esters of the polyphosphonates are likewise included. Specific examples include ethane-1-hydroxy 1,1-diphosphonic acid, methane diphosphonic acid, pentane-1-hydroxy-1,1-diphosphonic acid, methane dichloro diphosphonic acid, methane hydroxy diphosphonic acid, ethane-1-amino-1,1-diphosphonic acid, ethane-2-amino-1,1-diphosphonic acid, propane-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-N,N-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, propane-3,3-dimethyl-3-amino-1-hydroxy-1,1-diphosphonic acid, phenyl amino methane diphosphonic acid, N,N-dimethylamino methane diphosphonic acid, N(2-hydroxyethyl) amino methane diphosphonic acid, butane-4-amino-1-hydroxy-1,1-diphosphonic acid, pentane-5-amino-1-hydroxy- -1,1-diphosphonic acid, hexane-6-amino-1-hydroxy-1,1-diphosphonic acid and pharmaceutically acceptable esters and salts thereof.

In particular, the compounds of this invention may be combined with a mammalian estrogen agonist/antagonist. Any estrogen agonist/antagonist may be used as the second compound of this invention. The term estrogen agonist/antagonist refers to compounds which bind with the estrogen receptor, inhibit bone turnover and/or prevent bone loss. In particular, estrogen agonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and mimicking the actions of estrogen in one or more tissue. Estrogen antagonists are herein defined as chemical compounds capable of binding to the estrogen receptor sites in mammalian tissue, and blocking the actions of estrogen in one or more tissues. Such activities are readily determined by those skilled in the art of standard assays including estrogen receptor binding assays, standard bone histomorphometric and densitometer methods, and Eriksen

E. F. et al., Bone Histomorphometry, Raven Press, New York, 1994, pages 1-74; Grier S. J. et. al., The Use of Dual-Energy X-Ray Absorptiometry In Animals, Inv. Radiol., 1996, 31(1):50-62; Wahner H. W. and Fogelman I., The Evaluation of Osteoporosis: Dual Energy X-Ray Absorptiometry in Clinical Practice., Martin Dunitz Ltd., London 1994, pages 1-296). A variety of these compounds are described and referenced below.

Another preferred estrogen agonist/antagonist is 3-(4-(1,2-diphenyl-but-1-enyl)-phenyl)-acrylic acid, which is disclosed in Willson et al., Endocrinology, 1997, 138, 3901-3911. Another preferred estrogen agonist/antagonist is tamoxifen: (ethanamine,2-(-4-(1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl, (Z)-2-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1)) and related compounds which are disclosed in U.S. Pat. No. 4,536,516, the disclosure of which is incorporated herein by reference. Another related compound is 4-hydroxy tamoxifen, which is disclosed in U.S. Pat. No. 4,623,660, the disclosure of which is incorporated herein by reference.

A preferred estrogen agonist/antagonist is raloxifene: (methanone, (6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl)(4-(2-(1-piperidinyl)eth-oxy)phenyl)-hydrochloride) which is disclosed in U.S. Pat. No. 4,418,068, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is toremifene: (ethanamine, 2-(4-(4-chloro-1,2-diphenyl-1-butenyl)phenoxy)-N,N-dimethyl-- , (Z)-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) which is disclosed in U.S. Pat. No. 4,996,225, the disclosure of which is incorporated herein by reference. Another preferred estrogen agonist/antagonist is centchroman: 1-(2-((4-(-methoxy-2,2, dimethyl-3-phenyl-chroman-4-yl)-phenoxy)-ethyl)-p- yrrolidine, which is disclosed in U.S. Pat. No. 3,822,287, the disclosure of which is incorporated herein by reference. Also preferred is levormeloxifene. Another preferred estrogen agonist/antagonist is idoxifene: (E)-1-(2-(4-(1-(4-iodo-phenyl)-2-phenyl-but-1-enyl)-phenoxy)-ethyl)-pyrro- lidinone, which is disclosed in U.S. Pat. No. 4,839,155, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 2-(4-methoxy-phenyl)-3-[4-(2-piperidin-1-yl-ethoxy)-phenoxy]-benzo[b]thio- phen-6-ol which is disclosed in

U.S. Pat. No. 5,488,058, the disclosure of which is incorporated herein by reference.

Another preferred estrogen agonist/antagonist is 6-(4-hydroxy-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-naphthalen-2-- ol, which is disclosed in U.S. Pat. No. 5,484,795, the disclosure of which is incorporated herein by reference. Another preferred estrogen agonist/antagonist is (4-(2-(2-aza-bicyclo[2.2.1]hept-2-yl)-ethoxy)-phenyl)-(6-hydroxy-2-(4-hyd- roxy-phenyl)-benzo[b]thiophen-3-yl)-methanone which is disclosed, along with methods of preparation, in PCT publication no. WO 95/10513 assigned to Pfizer Inc. , the disclosure of which is incorporated herein by reference.

Other preferred estrogen agonist/antagonists include the compounds, TSE-424 (Wyeth-Ayerst Laboratories) and arazoxifene.

Other preferred estrogen agonist/antagonists include compounds as described in commonly assigned U.S. Pat. No. 5,552,412, the disclosure of which is incorporated herein by reference. Especially preferred compounds described therein are:

cis-6-(4-fluoro-phenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,- 7,8-tetrahydro-naphthalene-2-ol;

(-)-cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-te- trahydro-naphthalene-2-ol (also known as lasofoxifene);

cis-6-phenyl-5-(4-(2-pyrrolidin-1-yl-ethoxy)-phenyl)-5,6,7,8-tetrah- ydro-naphthalene-2-ol;

cis-1-(6'-pyrrolodinoethoxy-3'-pyridyl)-2-phenyl-6-hydroxy-1,2,3,4--tetrahydronaphthalene;

1-(4'-pyrrolidinoethoxyphenyl)-2-(4"-fluorophenyl)-6-hydroxy-1,2,3,- 4-tetrahydroisoquinoline;

is-6-(4-hydroxyphenyl)-5-(4-(2-piperidin-1-yl-ethoxy)-phenyl)-5,6,- 7,8-tetrahydro-naphthalene-2-ol; and

1-(4'-pyrrolidinolethoxyphenyl)-2-phenyl-6-hydroxy-1,2,3,4-tetrahyd-roisoquinoline.

Other estrogen agonist/antagonists are described in U.S. Pat. No. 4,133,814 (the disclosure of which is incorporated herein by reference). U.S. Pat. No. 4,133,814

discloses derivatives of 2-phenyl-3-aroyl-benzoth- iophene and 2-phenyl-3-aroylbenzothiophene-1-oxide.

Other anti-osteoporosis agents, which can be used in combination with a Formula I compound of the present invention, include, for example, the following: parathyroid hormone (PTH) (a bone anabolic agent); parathyroid hormone (PTH) secretagogues (see, e.g., U.S. Pat. No. 6,132,774), particularly calcium receptor antagonists; calcitonin; and vitamin D and vitamin D analogs.

Any compound that is an antihypertensive agent may be used in a combination aspect of this invention. Such compounds include amlodipine and related dihydropyridine compounds, calcium channel blockers, angiotensin converting enzyme inhibitors ("ACE-Inhibitors"), angiotensin-II receptor antagonists, beta-adrenergic receptor blockers and alpha-adrenergic receptor blockers. Such antihypertensive activity is determined by thoseskilled in the art according to standard tests (e.g. blood pressure measurements).

Amlodipine and related dihydropyridine compounds are disclosed in U.S. Pat. No. 4,572,909, which is incorporated herein by reference, as potent anti-ischemic and antihypertensive agents. U.S. Pat. No. 4,879,303, which is incorporated herein by reference, discloses amlodipine benzenesulfonate salt (also termed amlodipine besylate). Amlodipine and amlodipine besylate are potent and long lasting calcium channel blockers. As such, amlodipine, amlodipine besylate and other pharmaceutically acceptable acid addition salts of amlodipine have utility as antihypertensive agents and as antiischemic agents. Amlodipine and its pharmaceutically acceptable acid addition salts are also disclosed in U.S. Pat. No. 5,155,120 as having utility in the treatment of congestive heart failure. Amlodipine besylate is currently sold as Norvasc®.

Calcium channel blockers which are within the scope of this invention include, but are not limited to: bepridil, which may be prepared as disclosed in U.S. Pat. No. 3,962, 238 or U.S. Reissue No. 30,577; clentiazem, which may be prepared as disclosed in U.S. Pat. No. 4,567,175; diltiazem, which may be prepared as disclosed in U.S. Pat. No. 3,562, fendiline, which may be prepared as disclosed in U.S. Pat. No. 3,262,977; gallopamil, which may be prepared as disclosed in U.S. Pat. No. 3,261,859; mibefradil, prenylamine, semotiadil, terodiline, verapamil, aranipine, barnidipine, benidipine, cilnidipine, efonidipine,

elgodipine, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, cinnarizine, flunarizine, lidoflazine, lomerizine, bencyclane, etafenone, and perhexiline The disclosures of all such U.S. Patents are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: alacepril, which may be prepared as disclosed in U.S. Pat. No. 4,248,883; benazepril, which may be prepared as disclosed in U.S. Pat. No. 4,410,520; captopril, ceronapril, delapril, enalapril, fosinopril, imadapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril,. The disclosures of all such U.S. patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan, which may be prepared as disclosed in U.S. Pat. No. 5,196,444; eprosartan, which may be prepared as disclosed in U.S. Pat. No. 5,185,351; irbesartan, losartan, and valsartan. The disclosures of all such U.S. patents are incorporated herein by reference.

Beta-adrenergic receptor blockers (beta- or .beta.-blockers) which are within the scope of this invention include, but are not limited to: acebutolol, which may be prepared as disclosed in U.S. Pat. No. 3,857,952; alprenolol, amosulalol, which may be prepared as disclosed in U.S. Pat. No. 4,217,305; arotinolol, atenolol, befunolol, betaxolol; The disclosures of all such U.S. patents are incorporated herein by reference.

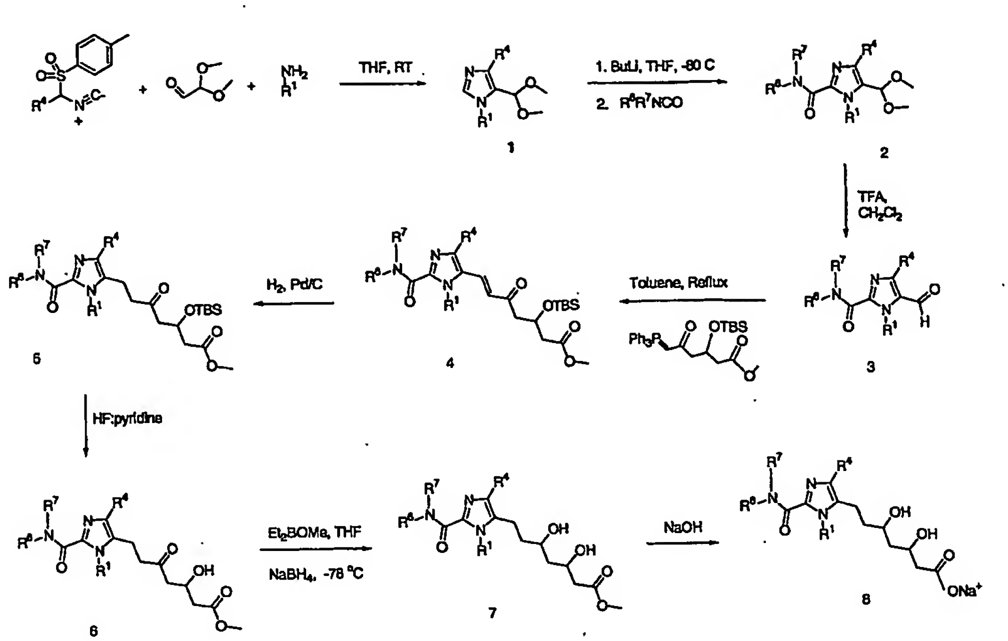
Alpha-adrenergic receptor blockers (alpha- or .alpha.-blockers) which are within the scope of this invention include, but are not limited to: amosulalol, which may be prepared as disclosed in U.S. Pat. No. 4,217,307; arotinolol, which may be prepared as disclosed in U.S. Pat. No. 3,932,400; dapiprazole, doxazosin, fenspiride, indoramin, labetolol, naftopidil, nicergoline, prazosin, tamsulosin, tolazoline, trimazosin, and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art. The disclosures of all such U.S. patents are incorporated herein by reference.

Any compound that is known to be useful in the treatment of Alzheimer's Disease may be used in a combination aspect of this invention. Such compounds include acetylcholine esterase inhibitors. Examples of known acetylcholine esterase inhibitors include donepezil (Aricept®), tacrine (Cognex®), rivastigmine (Exelon®) and galantamine (Reminyl). Aricept® is disclosed in the following U.S. patents, all of which are fully incorporated herein by reference: 4,895,841, 5,985,864, 6,140,321, 6,245,911 and 6,372,760. Exelon® is disclosed in U.S. Patent Nos. 4,948,807 and 5,602,176 which are fully incorporated herein by reference. Cognex® is disclosed in U.S. Patent Nos. 4,631,286 and 4,816,456 (fully incorporated herein by reference). Remynil® is disclosed in U.S. Patent Nos. 4,663,318 and 6,099,863 which are fully incorporated herein by reference.

PREPARATION OF COMPOUNDS OF THE INVENTION

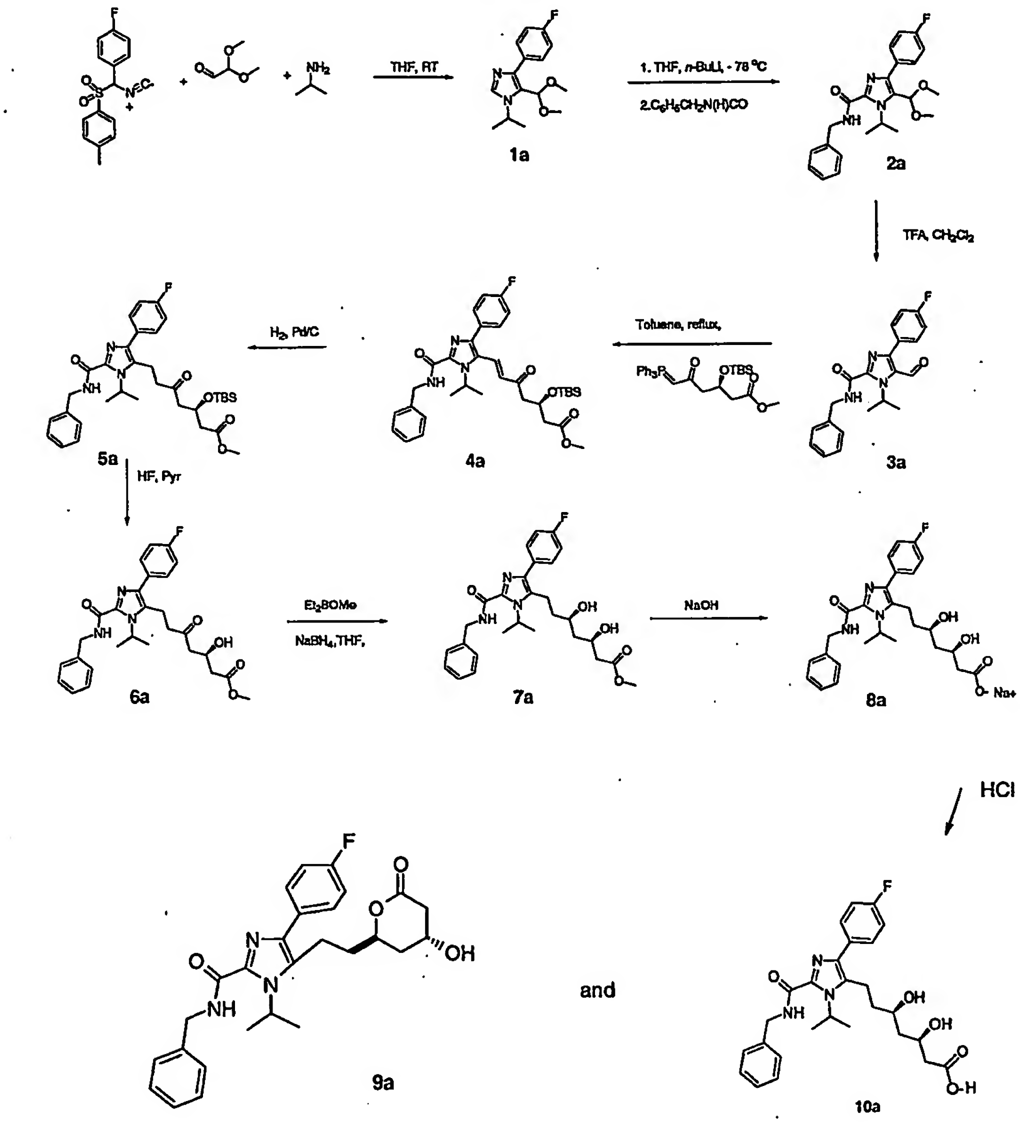
The present invention contains compounds that can be synthesized in a number of ways familiar to one skilled in organic synthesis. The compounds outlined herein can be synthesized according to the methods described below, along with methods typically used by a synthetic organic chemist, and combinations or variations of those methods, which are generally known to one skilled in the art of synthetic chemistry. The synthetic route of compounds in the present invention is not limited to the methods outlined below. It is assumed that one skilled in the art will be able to use the schemes below to synthesize compounds claimed in this invention. Individual compounds may require manipulation of the conditions in order to accommodate various functional groups. A variety of protecting groups known to one skilled in the art may be required. Purification, if necessary, may be accomplished on a silica gel column eluted with the appropriate organic solvent system. Also, reverse phase HPLC or recrystallization may be employed. The following non-limiting descriptions also demonstrate methods for the synthesis of compounds of the invention.

Scheme 1 shows the preparation of compounds of Formula I wherein -------- is absent and R^2 is $R^6R^7NC(O)$-.


THF, RT
1. BuLi, THF, -80 C
2. R⁶R⁷NCO
TFA, CH2Cl2
Toluene, Reflux
OTBS
H2, Pd/C
HF:pyridine
Et2BOMe, THF
NaBH4, -78 °C
NaOH
ONa+
1
2
3
4
5
6
7
8

Scheme 1

Scheme 1a shows a further example wherein ------ is absent, R^1 is isopropyl, R^2 is $R^6R^7NC(O)$-, one of R^6 and R^7 is H, the other one of R^6 and R^7 is benzyl and R^4 is 4-fluorophenyl.

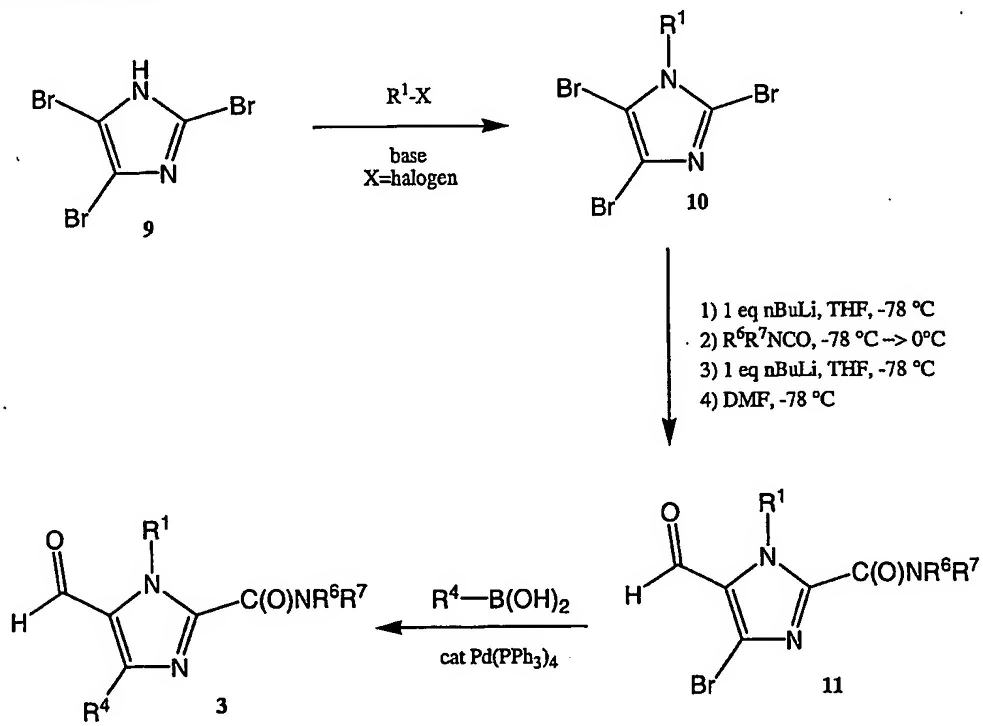


Scheme 1a

In Scheme 1a, compound **1a** is prepared by cycloaddition of 1-(isocyano-4-fluorophenyl-methanesulfonyl)-4-methyl-benzene with the imine formed *in situ* from the condensation of isopropyl amine with dimethoxy-acetaldehyde. (*J. Org. Chem.* 1998, *63*, 4529 and references therein) Treatment of compound **1a** with *n*-

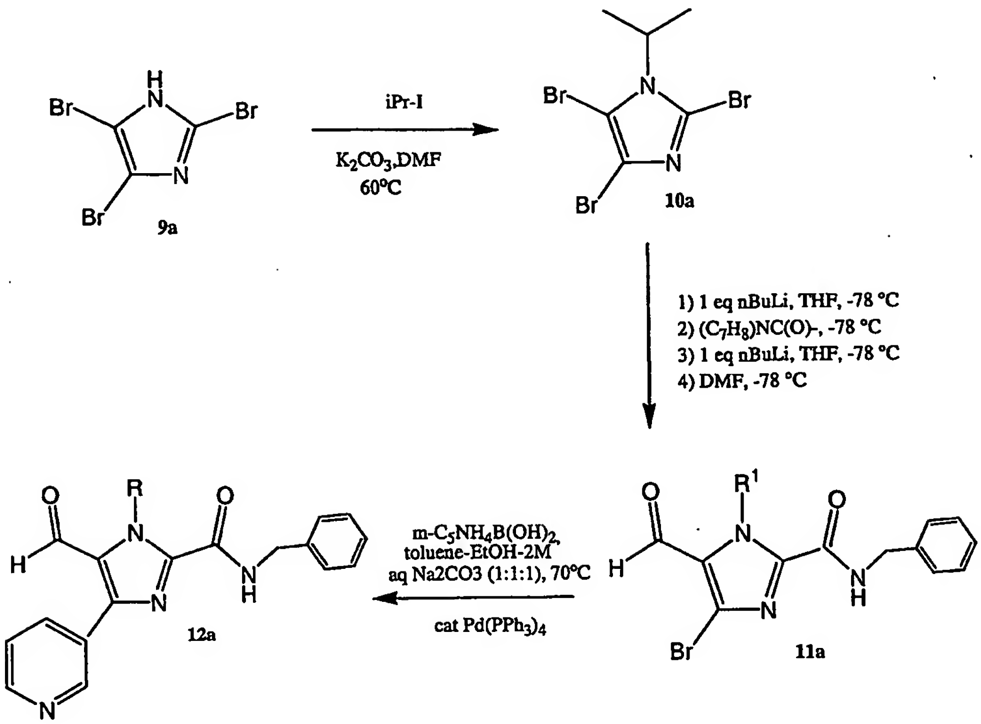
butyl lithium and reaction of the resulting 2-lithiated imidazole with benzyl isocyanate provides compound **2a**, which is deprotected under acidic conditions to give compound **3a**. Compound **4a** is obtained by condensation of compound **3a** and the optically active ylide (R)-3-(tert-Butyl-dimethyl-silanyloxy)-5-oxo-6-(triphenyl-λ^5-phosphanylidene)-hexanoic acid methyl ester (Konoike, T.; Araki, Y. *J. Org. Chem.* 1994, *59*, 7849). Catalytic hydrogenation of compound **4a** provides compound **5a** which is deprotected on treatment with hydrogen fluoride to give Compound **6a**. Diastereoselective reduction of compound **6a** with sodium borohydride in the presence of diethylmethoxyborane yields compound **7a**. Finally, compound **7a** is saponified with aqueous sodium hydroxide to give compound **8a**. Alternatively, one could work up the reaction under acidic conditions to provide the corresponding lactone 9a or to provide the corresponding free acid 10a.

Scheme 2 shows an alternate synthetic route to compound **3** of Scheme 1 (compound **4**, Scheme 2).



Scheme 2

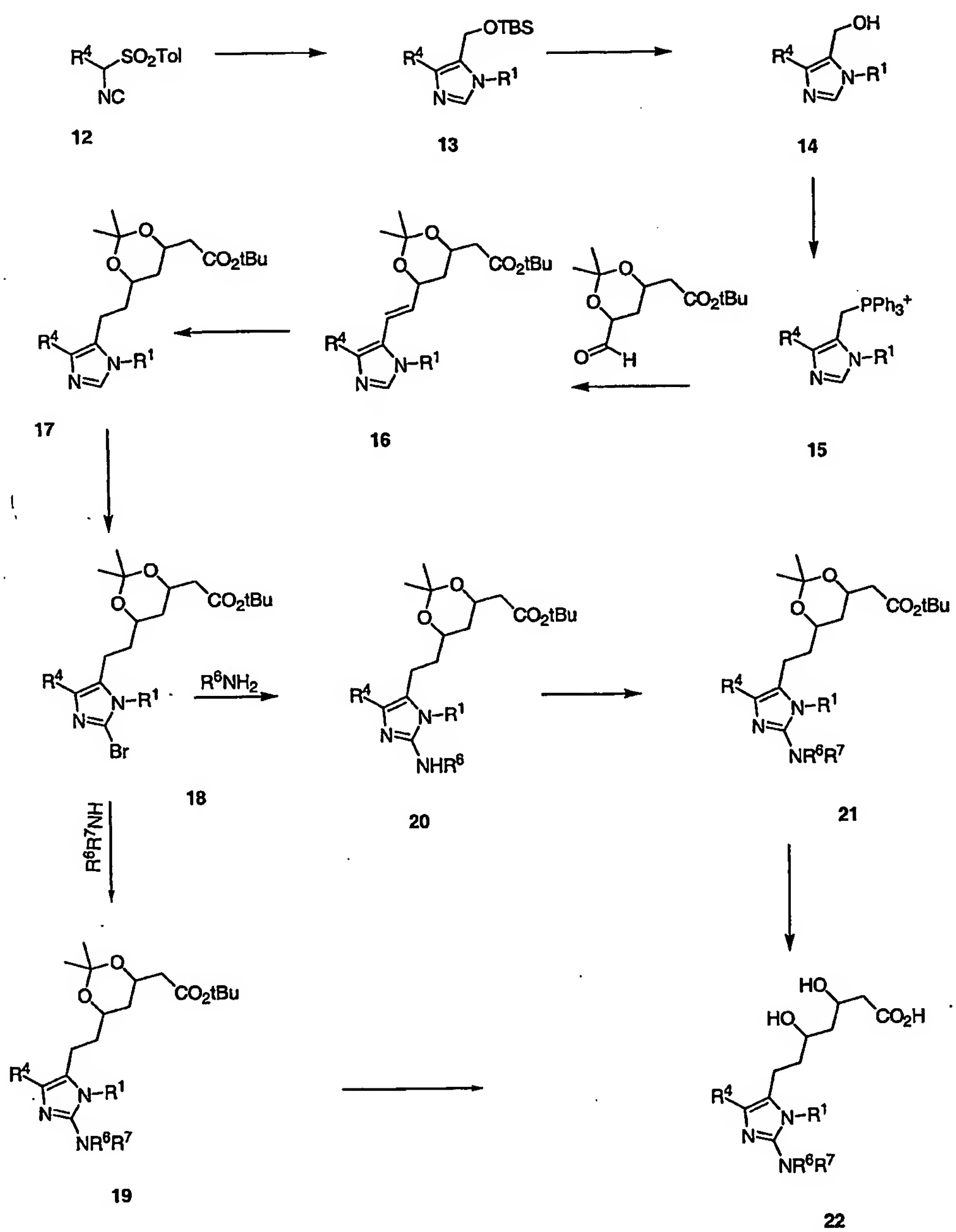
Scheme 2a shows a further example.



Scheme 2a

As shown in Scheme 2a, tribromoimidazole **9a** can be alkylated with isopropyl iodide to form N-alkyl imidazole **10a**. Treatment of tribromide **10a** with 1eq of n-butyllithium affords a 2-lithio-imidazole intermediate which undergoes reaction with benzylisocyanate. The resultant lithioamide is not isolated, but is treated with an additional 1 eq of n-butyllithium to affect lithiation at the 5-position. Treatment of this dianion with DMF affords, after workup, aldehyde **11a**. Bromide **11a** undergoes a Pd-catalyzed coupling with 3-pyridinyl-boronic acid to afford compound **12a**.

Scheme 3 shows the preparation of compounds of the invention wherein --------is absent and R^2 is $-(CH_2)_nNR^6R^7$ and n is 0.

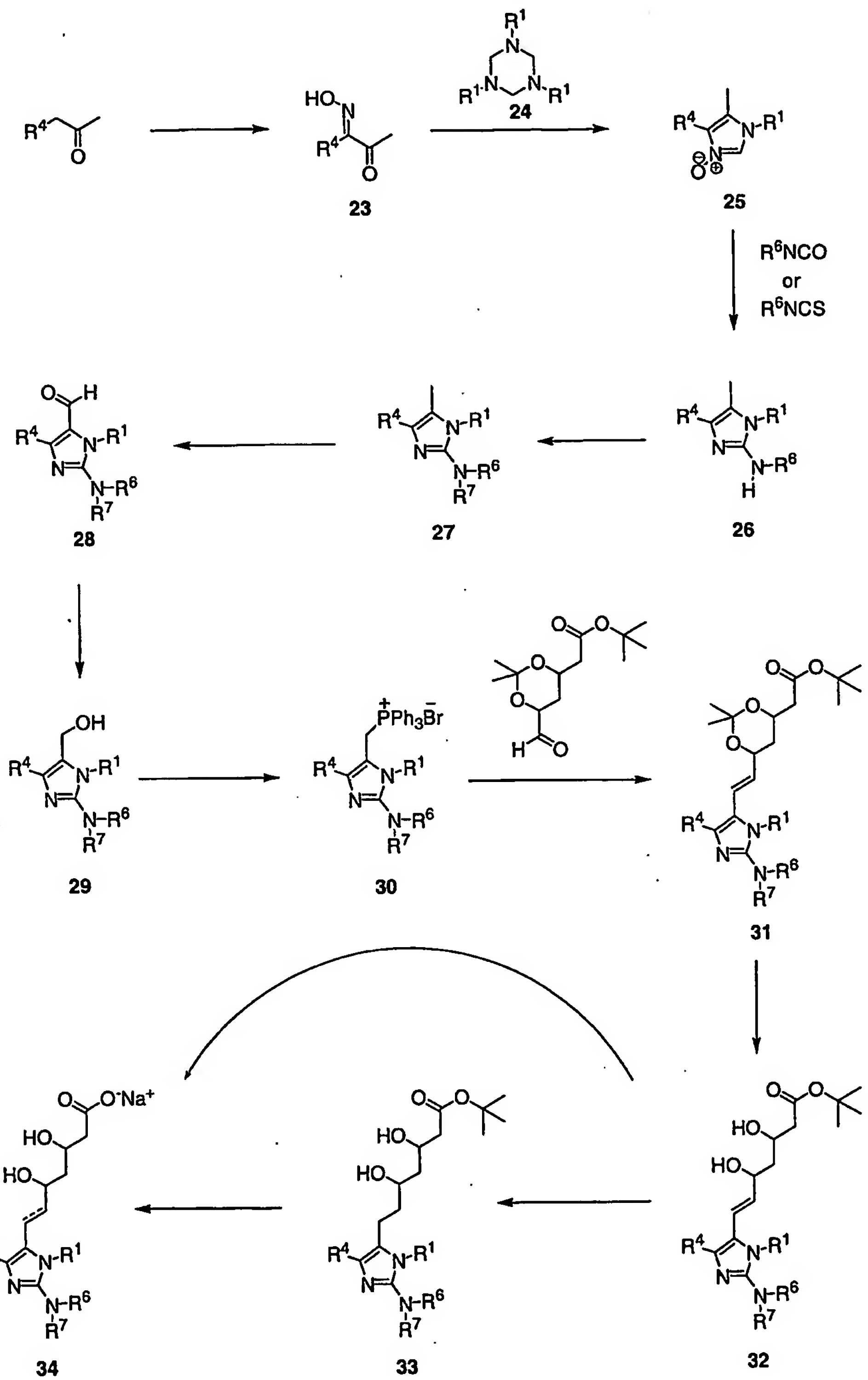


Scheme 3

As outlined in Scheme 3, condensation of isocyanides of formula **12** with $TBSOCH_2CHO$ and primary amines of formula R^1NH_2 can afford imidazoles of formula **13**. Deprotection of the silyl ether with acetic acid may then generate alcohols of formula **14**, which may then be converted to phosphonium salts of formula **15** with triphenylphosphine and HBr. Deprotonation of phosphonium salts of formula **15** with a suitable base such as n-butyllithium, for example,

followed by addition of an appropriate aldehyde can afford olefins of formula **16**, which may be reduced by catalytic hydrogenation to afford imidazoles of formula **17**. Bromination with N-bromosuccinimide may then produce bromides of formula **18**, which can be reacted with R^6R^7NH in the presence of an appropriate palladium catalyst to afford aminoimidazoles of formula **19**. Alternatively, compound **18** may be reacted with primary amines, to afford aminoimidazoles of formula **20**. Further reaction with an acylating or sulfonylating agent, such as R^7COCl, R^7NCO, R^7OCOCl or R^7SO_2Cl, can lead to the formation of acylated or sulfonylated amines. Cleavage of the ketal and tert-butyl ester protecting groups can then be accomplished with aqueous acid to afford the final products **22**.

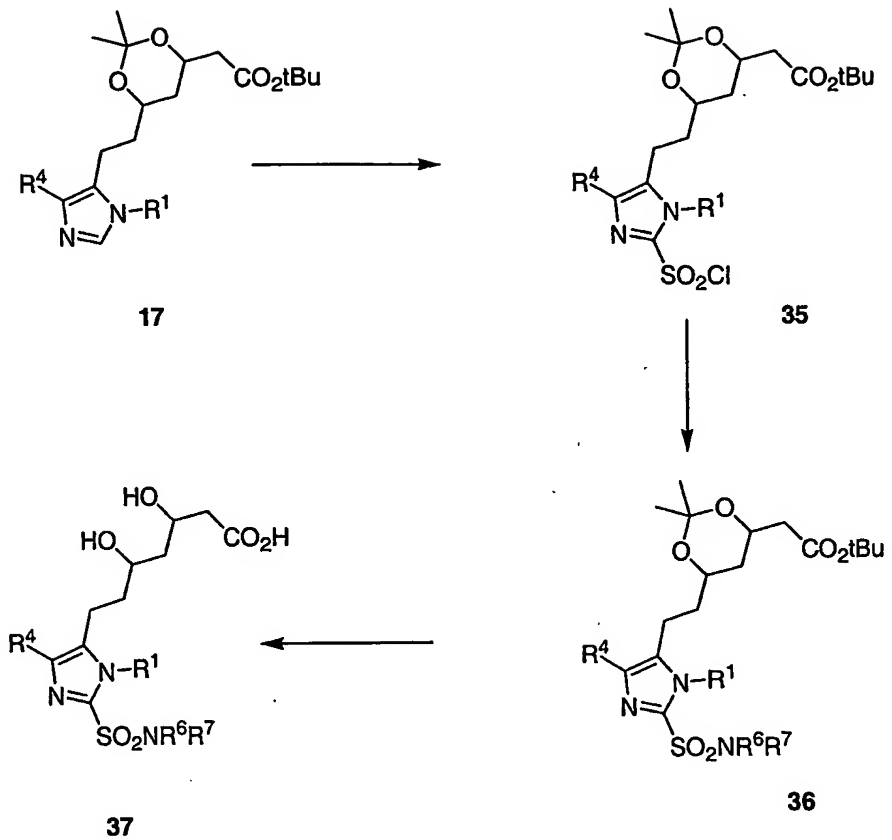
Scheme 3a shows an alternate route to similar compounds.



Scheme 3a

As shown in Scheme 3a, α-oximinoketones **23**, which can be prepared from their substituted acetone precursors via nitrosation with alkyl nitrites, for example, are converted to imidazole N-oxides **25** upon treatment with 1,3,5-trisubstituted hexahydro-1,3,5-triazines **24** which are either commercially available or prepared from amines R^1NH_2 and formaldehyde (*Helv. Chim. Acta* 1998, *81*, 1585, and references cited therein). Subsequent treatment with isocyanates or isothiocyanates R^6NCO or R^6NCS then affords the 2-aminoimidazoles **26** (*Tetrahedron* 2000, *56*, 5405, and references cited therein) which are reacted with an acylating or sulfonylating agent, such as R'COCl, (R'CO)O or R'SO2Cl, to give imidazoles **27**. Oxidation of the 5-methyl group with ceric ammonium nitrate introduces the aldehyde functionality which is then reduced with lithium tri-*tert*-butoxyaluminum hydride, for example, to afford the alcohol intermediates **29**. Reaction with triphenylphosphine hydrobromide provides the phosphonium salts **30** which are then deprotonated with a suitable base such as n-butyllithium or sodium bis(trimethylsilyl)amide and treated with 6-formyl-2,2-dimethyl-[1,3]dioxan-4-yl)acetic acid tert-butyl ester (or *tert*-butyl 6-oxo-3,5-O-isopropylidene-3,5-dihydroxyhexanoate) [optically active form, (4R,6S)-6-formyl-2,2-dimethyl-[1,3]dioxan-4-yl)acetic acid tert-butyl ester, prepared as in *Syn. Comm.* 2003, *33(13)*, 2275-83)] to give the Wittig products **31** as mixtures of *cis/trans* olefin isomers. The acetonide protecting group is then cleaved in the presence of aqueous acid to give diols **32**, and the olefin is then reduced by catalytic hydrogenation over palladium on carbon, for example, to afford intermediates **33**. Saponification with aqueous sodium hydroxide then provides the final products **34** wherein ------ is absent. Alternatively, the *cis/trans* olefin isomers **32** can be separated by chromatography and the saponification carried out to give the final products **34** wherein ------ is a bond. One might also convert aldehyde **28** to the final product **34** using the method described in Scheme 1.

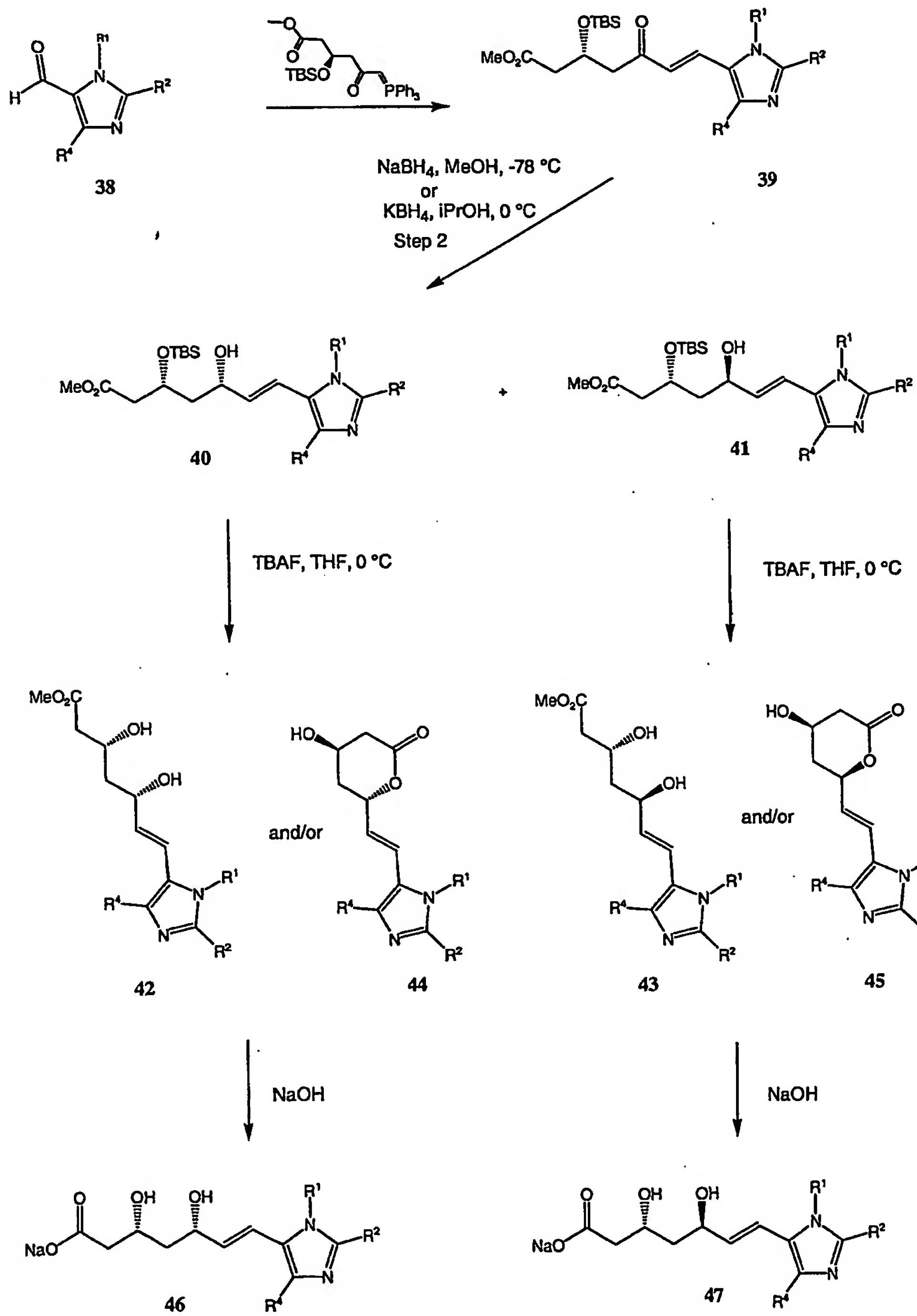
Scheme 4 shows the preparation of compounds of the invention wherein -------- is absent and R^2 is $SO_2NR^6R^7$, starting with compound **17**.



Scheme 4

As outlined in Scheme 4, deprotonation of compound **17** with n-butyllithium followed by quenching with sulfur dioxide gas and subsequent exposure to n-chlorosuccinimide can afford chlorosulfonyl imidazoles of formula **35**. Addition of various amines can then generate sulfonamides of formula **36**. Cleavage of the ketal and tert-butyl ester protecting groups can then be accomplished with aqueous acid to afford the final product **37**.

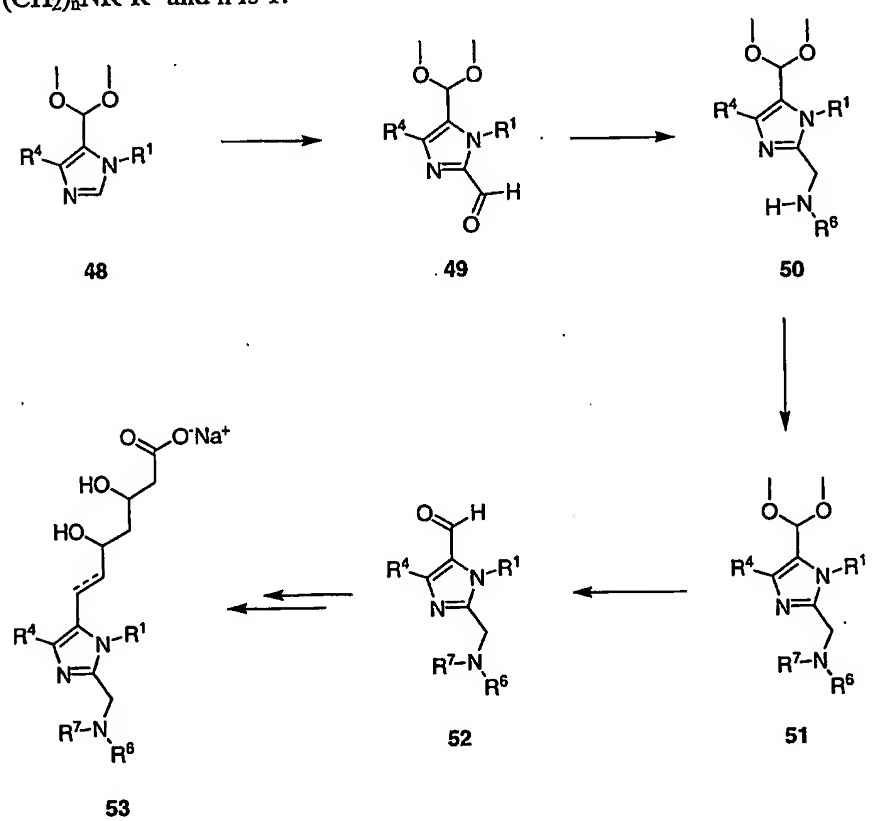
Scheme 5 shows the preparation of compounds of the invention wherein ——— is a bond.



Scheme 5

As depicted in Scheme 5, step 1, a suitable 5-formyl-1,2,4-trisubstituted imidazole **38** can be reacted with ylide (3*R*)-3-(*tert*-butyldimethylsiloxy)-5-oxo-6-triphenylphosphoranylidenehexanoate to afford enone **39**. In step 2, reduction of enone **39** with sodium or potassium borohydride affords a separable mixture of epimeric alcohols **40** and **41**. Solvents for this transformation include methanol and isopropanol at temperatures between –78 °C and 0 °C. In step 3, treatment of silyl ethers **40** or **41** with tetrabutylammonium fluoride affords the diols **42** or **43** respectively. Depending on the reaction time and temperature, lactones **44** or **45** may be further formed from methyl esters **42** or **46** during step 3. The mixtures of methyl esters and lactones may be separated or may be used together in the final saponification. Accordingly, in step 4, treatment of **42** [and/or **44**] or **46** [and/or **45**] with aqueous sodium hydroxide affords sodium salts **46** or **47** respectively.

Scheme 6 shows the preparation of compounds of the invention wherein R^2 is –$(CH_2)_nNR^6R^7$ and n is 1.



Scheme 6

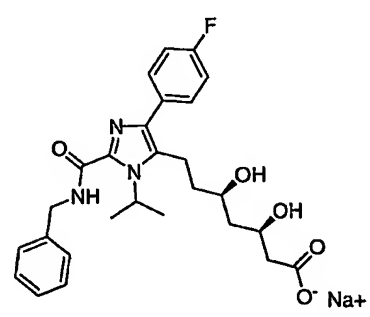
As outlined in Scheme 6, imidazole-2-carboxaldehydes **49** can be prepared from imidazoles **48** (prepared as in Scheme 1) by treatment with a base such as n-butyllithium or lithium diisopropylamide and reaction of the resulting 2-lithiated imidazole with N,N-dimethylformamide. Reductive amination with amines R^6NH_2 then affords the 2-(aminomethyl)imidazoles **50** which can be acylated or sulfonylated as in Scheme 3a to provide intermediates **51**. Alternatively, imidazole-2-carboxaldehydes **49** can be converted to their oxime derivatives upon treatment with hydroxylamine hydrochloride and then reduced under catalytic hydrogenation conditions, for example, to give 2-(aminomethyl)imidazoles **50** wherein R^6 is H. Deprotection of the acetals **51** under acidic conditions gives the 5-formylimidazoles **52** which are converted to the final products **53** using the methods described in Scheme 3a for the conversion of structures **28** to their final products **34.**

EXAMPLES

The following non-limiting Examples show how to carry out the present invention. The synthetic route of compounds of the present invention is not limited to the methods outlined below. It is assumed that one skilled in the art will be able to use the schemes outlined below to synthesize compounds claimed in this invention. Example 1 shows the preparation of a compound of Formula I wherein wherein R^1 is isopropyl, R^2 is $R^6R^7NC(O)$- and R^4 is 4-fluorophenyl. In Example 1, one of R^6 and R^7 is H and the other one of R^6 and R^7 is benzyl. Compounds with variations on R^6 and R^7 were made using a similar reaction scheme and are shown, along with characterizing data, in TABLE I which follows Example 1.

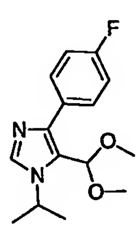
Example 1

(3*R*,5*R*)-7-[2-benzylcarbamoyl-5-(4-fluorophenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid sodium salt.



Step A

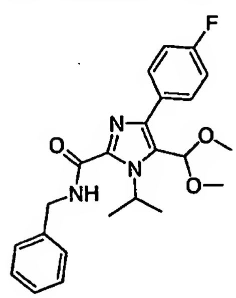
<u>5-Dimethyoxymethyl-4-(4-fluoro-phenyl)-1-isopropyl-1*H*-imidazole</u>



A solution of dimethoxy-acetaldehyde (7.2 mL, 28 mmol, 45% in methyl-tert-butyl ether, Fluka Chem.) and isopropyl amine (5.7 mL, 67 mmol, Aldrich Chemical Co.), in anhydrous tetrahydrofuran (90 mL), was stirred, under a nitrogen atmosphere and at ambient temperature, for approximately 3 hrs. To this solution was added 1-(isocyano-4-fluorophenyl-methanesulfonyl)-4-methyl-benzene (6.44 g, 22 mmol). The resulting mixture was stirred for 18 h at ambient temperature, then concentrated *in vacuo* to 30% initial volume. The reaction mixture was diluted with water (20mL) and extracted (2x) with ethyl acetate. The combined extracts were washed with sodium hydroxide solution (20 mL, 1 molar) and dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to a yellow oil and chromatographed on silica (10 to 80% ethyl acetate in hexanes) to yield 4.88 g of light yellow amorphous powder. Low resolution mass spectroscopy (APCI) *m/z* 279 $[M + H]^+$.

Step B

<u>5-Dimethoxymethyl-4-(4-fluoro-phenyl)-1-isopropyl-1H-imidazole-2-carboxylic acid benzylamide</u>

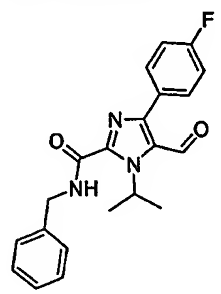


To a stirred solution of 5-Dimethyoxymethyl-4-(4-fluoro-phenyl)-1-isopropyl-1*H*-imidazole (1.07g, 3.8 mmol), in anhydrous tetrahydrofuran (15 mL), cooled to -78 C, was added *n*-butyllithium (2.9 mL, 2.0 M in pentane) via syringe while maintaining the temperature below -70° C. The mixture was stirred for 30 min. 1-Fluoro-4-isocyanatomethyl-benzene (0.863 mL, 7.7 mmol) was added and the reaction miexture was allowed to warm to ambient temperature over 30 min. Saturated sodium bicarbonate solution (20 mL) was added and mixture was extracted with ethyl acetate (2 x 15 mL). The combined extracts were concentrated *in vacuo* to a yellow slurry. The slurry was triturated with 1-

propanol and the solid precipitate was removed by vacuum filtration washing with 1-propanol. The filtrate was concentrated *in vacuo* to give a yellow oil that was purified by chromatography on silica (10 to 60% ethyl acetate in hexanes) and concentrated *in vacuo* to yield 1.2 g of desired product as a light yellow powder. Low resolution mass spectroscopy (APCI) *m/z* 412 $[M + H]^+$.

Step C

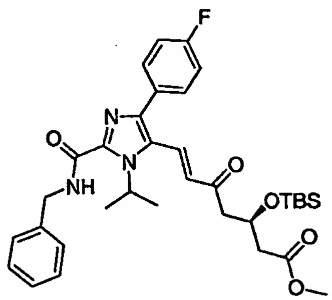
4-(4-Fluoro-phenyl)-5-formyl-1-isopropyl-1H-imidazole-2-carboxylic acid benzylamide



5-Dimethoxymethyl-4-(4-fluoro-phenyl)-1-isopropyl-1-*H*-imidazole-2-carboxylic acid 4-fluoro-benzylamide (1.2 g., 2.9 mmol) were dissolved in a mixture of trifluoroacetic acid 10% methylene chloride (10 mL) and stirred at room temperature for 2 hours. The solution was concentrated *in vacuo* to 10% initial volume and sodium hydroxide (40 mL., 1 molar) was added. The mixture was extracted with methylene chloride (3 x 15 mL). The extracts were combined, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give 1.0 g. of the desired product as an off-white amorphous powder. Low resolution mass spectroscopy (APCI) *m/z* 366 $[M + H]^+$.

Step D

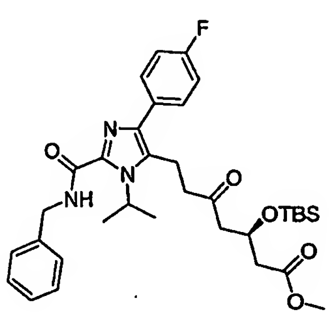
(R)-7-[2-Benzylcarbamoyl-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-hept-6-enoic acid methyl ester



A solution of 4-(4-Fluoro-phenyl)-5-formyl-1-isopropyl-1H-imidazole-2-carboxylic acid 4-fluoro-benzylamide (1.16 g., 3.2 mmol) and (R)-3-(tert-Butyl-dimethyl-silanyloxy)-5-oxo-6-(triphenyl-l5-phosphanylidene)-hexanoic acid methyl ester (2.5 g, 4.8 mmol) in toluene (15 mL) was heated to reflux for 24 hours under nitrogen atmosphere. The cooled mixture was concentrated *in vacuo* to give a crude oil, which was purified by chromatography on silica (15 to 60% ethyl acetate in hexanes) to give the desired product as a colorless glass. Low resolution mass spectroscopy (APCI) *m/z* 622 $[M+H]^+$. 1H NMR (400 MHz, CHLOROFORM-D) δppm 0.0 (d, *J*=3.4 Hz, 2 H) 0.1 (m, 4H) 0.8 (m, 10 H) 1.7 (m, 8H) 2.5 (m, 2H) 2.6 (m, 2H) 3.1 (m, 1H) (d, *J*=3.9 Hz, 3H) 3.7 (s, 1H) 4.6 (m 3H) 7.1 (m, 2H) 7.3 (m, 2H) 7.3 (d, *J*=5.9 Hz, 4H) 7.5 (m, 1H) 7.6 (d, *J*=3.4 Hz, 1H)

Step E

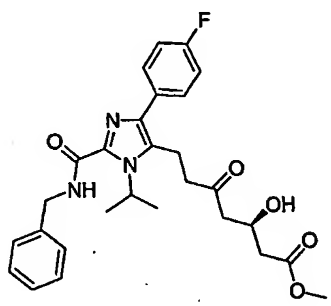
<u>(R)-7-[2-Benzylcarbamoyl-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-heptanoic acid methyl ester</u>



The product from Step D was hydrogenated in tetrahydrofuran using (0.2g) 10% Pd/C and hydrogen atmosphere (4295 psi per mol) for 13.3 hours. The mixture was filtered through celite and concentrated *in vacuo* to yield 0.862 g. of desired product as a light yellow glass. Low resolution mass spectroscopy (APCI) *m/z* 624 $[M + H]^+$.

Step F

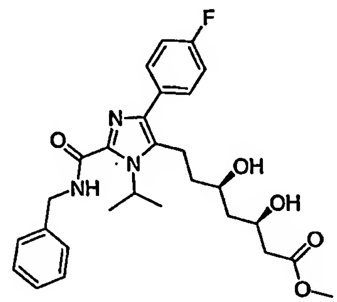
(R)-7-[2-Benzylcarbamoyl-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3-hydroxy-5-oxo-heptanoic acid methyl ester



An ice cold solution of (R)-7-[2-Benzylcarbamoyl-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-heptanoic acid methyl ester (0.862 g, 1.4 mmol) in anhydrous THF (12 mL) in a 50 mL conical polypropylene tube was treated with hydrogen fluoride-pyridine (3 mL, 70% HF) The mixture was warmed to ambient temperature and stirred for 2 hours. The reaction mixture was adjusted to pH 11 with sodium carbonate solution (40 mL, 1 molar). The mixture was diluted with water and extracted (3 x 15 mL) with ethyl acetate. The extracts were combined, washed sequentially with saturated sodium bicarbonate solution (15 mL) and brine (15 mL), and dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to yield 757 mg of product as an amber glass. Low resolution mass spectroscopy (APCI) *m/z* 510 $[M + H]^+$. ^1H NMR (400 MHz, CHLOROFORM-D) δppm 1.4 (s, 1H) 1.7 (m, 7H) 2.5 (m, 2H) 2.6 (m, 1H) 2.7 (m, 1H) 3.1 (d, *J*=8.3 Hz, 2H) 3.7 (m, 3H) 4.4 (s, 1H) 4.6 (d, *J*=6.1 Hz, 2H) 7.1 (t, *J*=8.7 Hz, 2H) 7.3 (m, 6H) 7.5 (dd, *J*=8.8 Hz, 5.4 Hz, 2H) 7.9 (s, 1H)

Step G

(3R,5R)-7-[2-Benzylcarbamoyl-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid methyl ester



A solution of (R)-7-[2-(benzylcarbamoyl)-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3-hydroxy-5-oxo-heptanoic acid methyl ester (643 mg., 1.3 mmol) in anhydrous tetrahydrofuran (5 mL) was cooled to -74° C under a nitrogen atmosphere. Diethylmethoxyborane (0.497 mL, 3.79 mmol, Aldrich Chemical Co.) was added dropwise and the solution and stirred 60 minutes at -74° C. Sodium borohydride (67 mg., 1.8 mmol) was added, neat, and stirring was continued at -75° C for 1.5 hours. 6 drops of glacial acetic acid were added and the mixture was warmed to ambient temperature. Added ethanol amine (0.457mL, 7.6 mmol Aldrich) to decomplex boron, stirring 18 hours at RT. The reaction mixture was washed with sat. sodium bi-carbonate solution (15 mL,) and extracted three times with methylene chloride. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated to a crude oil. The product was purified by chromatography on silica (10 to 60% ethyl acetate in hexanes) to give 574 mg of desired product as a colorless glass. Low resolution mass spectroscopy (APCI) *m/z* 512 $[M + H]^+$. ^1H NMR (400 MHz, CHLOROFORM-D) δppm 1.4 (m, 1H) 1.6 (m, 1H) 1.7 (d, *J*=7.1 Hz, 6H) 1.8 (m, 1H) 1.9 (m, 1H) 2.6 (m, 1H) 2.9 (m, 1H) 3.2 (m, 1H) 3.7 (s, 3H) 4.0 (m, 1H) 4.4 (m, 1H) 4.6 (d, *J*=6.1 Hz, 2H) 5.3 (m, 1H) 7.1 (m, 2H) 7.3 (m, 1H) 7.3 (m, 4H) 7.6 (m, 2H) 8.0 (t, *J*=6.0 Hz, 1H)

Step H

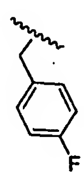
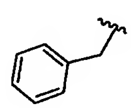
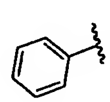
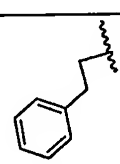
(3*R*,5*R*)-7-[2-benzylcarbamoyl-5-(4-fluorophenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid sodium salt.

A stirred solution of (3R, 5R)-7-[2-(benzylcarbamoyl)-5-(4-fluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid methyl ester (574 mg., 1.12 mmol) in THF (1 mL) and water (1 mL) was treated with sodium hydroxide (1.07 mL, 1 molar). The resulting solution was stirred at room temperature for 2 hours. Water (30 mL) was added and the mixture was lyophilized to yield 496 mg of desired final product as a fluffy white powder. Low resolution mass spectroscopy (APCI) *m/z* 498 $[M + H]^+$.

Compounds with variations on R^6 and R^7 were made using a similar reaction scheme as shown in Ex. 1 and representative compounds are shown, along with characterizing data, in Table I.

TABLE I

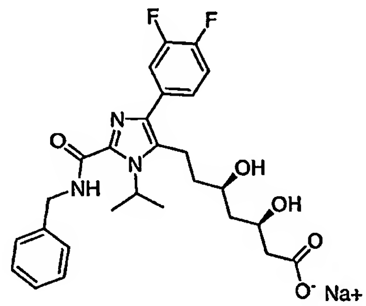
Variations On Example 1

R^6	R^7	MS	Theory			Found		
			C	H	N	C	H	N
H,		516 (APCI +)	50.71	6.25	6.57	50.31	5.92	6.29
H,		498	59.33	6.27	7.69	59.66	6.10	7.30
H,		484	49.89	5.57	6.71	49.52	5.26	6.46
H,		512	53.30	6.45	6.66	52.94	6.06	6.48

Example 2 shows the preparation of a compound of Formula I wherein R^1 is isopropyl, R^2 is benzylcarbamoyl- and R^4 is difluorophenyl. Compounds with variations on R^4 were made using a similar reaction scheme and are shown, along with characterizing data, in TABLE II which follows Example 2.

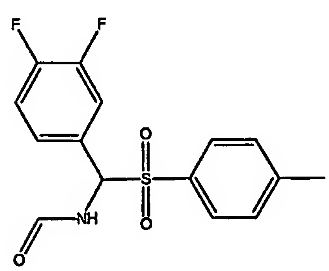
Example 2

(3*R*,5*R*)-7-[2-benzylcarbamoyl-5-(3,4-difluoro-phenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid sodium salt



Step A

<u>*N*-[(3,4-Difluoro-phenyl)-(toluene-4-sulfonyl)-methyl]-formamide</u>

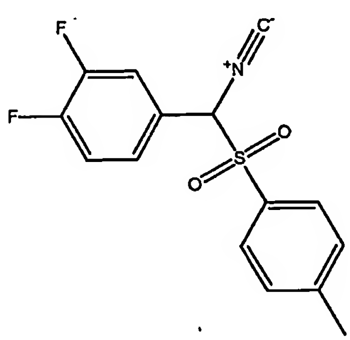


Sulfinic acid sodium salt dihydrate (21.4 g, 95 mmol) and formamide (4.28 g., 95.0 mmol, Aldrich Chemical Co.), were combined in a 1L, 3- neck flask. Positive nitrogen gas pressure was applied and 500 mL dry acetonitrile was added. The mixture was stirred to form a slurry and neat 3,4-difluorobenzaldehyde (9.0 g, 63.33 mmol) was added in one portion. The flask was cooled to 12° C on water-ice bath, and chlorotrimethylsilane (28.13 mL, 221.7 mmol) was added via a pressure equalized addition funnel, maintaining temperature below 25° C for the

addition (approx. 20 min). The mixture was slowly warmed to RT and stirred for 48 hrs. The heterogeneous mixture was treated with water (1.2L) and the resulting suspension was stirred for 30 min. The solids were isolated by filtration and the resulting filter cake was washed with water (500 mL). The solids were dried in a vacuum oven at 50° C at 27 inches of Hg for 24 hours to give the product, 18.2 g of a white solid. Low resolution mass spectroscopy (APCI) *m/z* 326 $[M + H]^+$.

Step B

<u>1,2-Difluoro-4-[isocyano-(toluene-4-sulfonyl)-methyl]-benzene</u>



<u>Caution Reagent may be unstable above 40°C.</u>

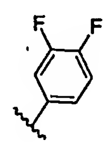
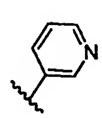
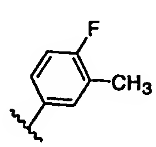
A mechanically stirred suspension of *N*-[(3,4-Difluoro-phenyl)-(toluene-4-sulfonyl)-methyl]-formamide (18.2 g., 55.9 mmol) in anhydrous tetrahydrofuran (150 mL) was treated with phosphorus oxychloride (8.2 mL, 89.5 mmol). The solution was stirred for 10 – 15 min. and then cooled to between -5° C and 0° C. Triethylamine (37.4 mL., 268.5 mmol) was added dropwise to the slurry over 45 min. at such a rate as to keep the reaction temperature below 0° C but above -5° C. After complete triethylamine addition, the yellowish-brown slurry was stirred for 30 min. at 0° C. The reaction mixture was diluted with chilled ethyl acetate (100 mL) and water (50 mL), stirred for 10 min. near 10° C, and transferred to a separatory funnel. The aqueous layer was removed, and the organic phase was washed with water (2 x 100 mL), saturated sodium bicarbonate solution (100 mL), and water (100 mL) again. The organic phase was concentrated under vacuum

until 10 – 15% of the initial volume remained. 1-Propanol (100 mL) was added, and the solution was concentrated again under vacuum at 35° C until 10% of the initial volume remained. The solution was allowed to stand 40 min. at 4 - 8° C, and the fine yellow precipitate which was formed was collected by vacuum filtration and rinsed with 1-propanol (30 mL). The off-white solid was dried to a constant weight under vacuum to yield 4.3 g of desired product. Low resolution mass spectroscopy (APCI) *m/z* 308 $[M + H]^+$. The remaining steps were carried out in a similar manner as Steps A-H of Example 1.

Compounds with variations on R^4 were made using a similar reaction scheme as shown in Ex. 2, and representative compounds are shown, along with characterizing data, in Table II.

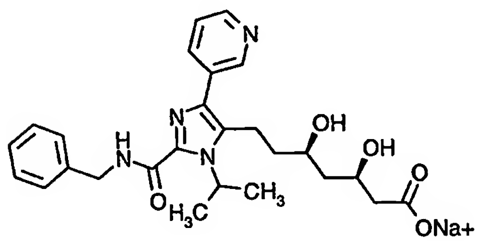
TABLE II

Variations On Example 2

R^4	MS	Theory			Found		
		C	H	N	C	H	N
	516 (APCI+)	58.03	5.84	7.52	58.35	5.78	7.12
	418	62.14	6.22	11.1	57.12	6.17	9.77
	530	57.06	6.16	7.13	57.44	5.96	6.73

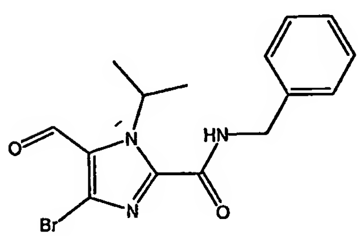
Example 3

(3R,5R)-7-(2-Benzylcarbamoyl-3-isopropyl-5-pyridin-3-yl-3H-imidazol-4-yl)-3,5-dihydroxy-heptanoic acid sodium salt



Step A

<u>4-Bromo-5-formyl-1-isopropyl-1H-imidazole-2-carboxylic acid benzylamide</u>

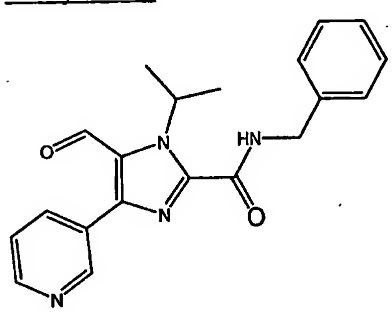


A solution of 2, 4, 5 Tribromo-1-isopropyl-1H-imidazole (2.0 g, 5.8 mmol) (Prepared from tribromoindole, iPrI/K_2CO_3/DMF/60°C) in dry THF (20 mL), cooled to – 78 °C (dry ice-acetone bath) under a nitrogen atmosphere, was treated with n-Butyl lithium (3.91 mL, 6.05 mmol, 1.6 M in hexanes). The resulting solution was allowed to stir at –78 °C for 5 minutes, then treated with benzyl isocyanate (0.71 mL, 5.8mmol). The reaction mixture was stirred at –78 °C for 10 minutes at which time the cooling bath was replaced with an ice water bath. After 20 minutes an analysis of the reaction mixture by loop injection mass spectroscopy indicated a new mass corresponding to the expected addition product: MS APCI 401.9 [M+H]. The reaction mixture was recooled to –78 °C and treated with an additional equivalent n-butyl lithium (3.91 mL, 6.05 mmol, 1.6 M in hexanes). The solution was allowed to stir at –78 °C for 5 minutes, then treated with DMF (0.89 mL, 11.53 mmol). was added and stirred cold for 15

minutes The reaction mixture was stirred at –78 °C for 10 minutes at which time the cooling bath was replaced with an ice water bath. After 30 minutes the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, washed with sat. NH_4Cl and brine, dried ($MgSO_4$), and concentrated to give a yellow solid. Purification by flash chromatography (SiO_2, ethyl acetate/hexanes 1:19 to 1:4) provided the desired product as a colorless solid; yield: 1.24 g (61.4%); mp = 128-129 °C (ethyl acetate-hexanes), MS APCI 350, 352 [M+H].

Step B

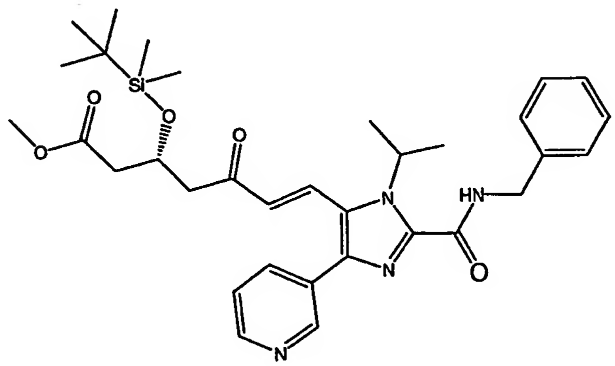
5-Formyl-1-isopropyl-4-pyridin-3-yl-1H-imidazole-2-carboxylic acid benzylamide



A mixture of 4-Bromo-5-formyl-1-isopropyl-1H-imidazole 2-carboxylic acid benzyl amide (0.87 g, 2.48 mmol) in toluene/ethanol/2M Na_2CO_3 (15 mL, 1:1:1) was sparged briefly with argon then treated with 3-pyridyl boronic acid (0.37 g, 2.98 mmol) and palladium tetrakistriphenyl phosphine (0.14 g, 0.12 mmol). The resulting mixture was heated to 70°C for 12 h. Analysis by TLC (5% MeOH / DCM) indicated complete consumption of the starting material. The reaction mixture was diluted with ethyl acetate, the organic layer was separated, washed (2X) with sat. $NaHCO_3$, washed with brine, dried (Na_2SO_4) and concentrated to give a yellow oil. Purification by flash chromatography (SiO_2, CH_2Cl_2/methanol 100:0 to 97:3) gave the desired product as a colorless solid; yield: 0.59 g (68 %); MS APCI 349 [M+H], 1H NMR ($CDCl_3$) δ (9.86 s, 1H), (8.84 d, J = 2.2 Hz, 1H), (8.68 d, J = 4.8 Hz, 1H), (8.04 bs, 1H), (7.93 d, 1H), (7.67 m, 1H), (7.54-7.28 m, 5H), (6.35 m, 1H), (4.62 d, J = 6.1 Hz, 2H), (1.63 d, J = 7.1 Hz, 6H).

Step C

7-(2-Benzylcarbamoyl-3-isopropyl-5-pyridin-3-yl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-hept-6-enoic acid methyl ester



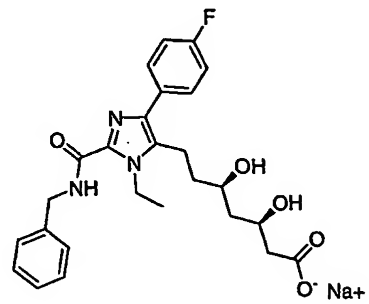
A solution of 5-Formyl-1-isopropyl-4-pyridin-3yl-1H imidazole-2-carboxylic acid bezyl amide (0.55 g, 1.58 mmol) and 3-(tert-Butyl-dimethyl-silanyloxy)-5-oxo-6-(triphenyl-l5-phosphanylidene)-hexanoic acid methyl ester (0.89 g, 1.66 mmol) in toluene (10 mL) was heated to reflux overnight. The solvent was removed *in vacuo* to give an orange oil (1.74 g). Purification by flash chromatography (SiO_2, CH_2Cl_2/hexanes/MeOH 80:20:0 to 97:0:3:3) gave a orange oil that was triturated (hexanes-ethyl acetate) and filtered to remove triphenylphosphine oxide; yield: 0.98g (100%); MS APCI 605 [M+H]. ^{1}H NMR ($CDCl_3$) δ (8.81 dd, J = 2.2, 0.7 Hz, 1H), (8.60 dd, J = 4.9, 1.7 Hz, 1H), (7.85 s, 1H), (7.85 d, J = 0.49 Hz, 1H), (7.73-7.65 m, 3H), (7.56-7.53 m, 1H), (7.49-7.45 m, 1H), (7.37-7.32 m, 7H), (6.34 d, J = 15.9 Hz, 1H), (6.10 bs 1H), (4.60 d, J = 6.1 Hz, 3H), (3.67 s, 3H), (2.72 m, 2H), (2.50 m, 2H), (1.65 d, J = 7.1 Hz, 6H), (0.81 s, 9H), (0.05, s, 3H), (0.00 s, 3H); * although material was contaminated with triphenylphosphine oxide it was used as is in subsequent reaction.

The remaining steps were carried out in a similar manner as Steps E-H of Example 1.

Example 4 shows the preparation of a compound of Formula I wherein R^1 is ethyl, R^2 is benzyl carbamoyl- and R^4 is 4-fluorophenyl. Compounds with variations on R^1 are shown in TABLE III which follows Example 4.

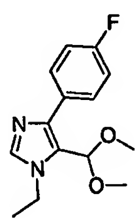
Example 4

3R,5R)-7-[2-benzylcarbamoyl-3-ethyl-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid sodium salt



Step A

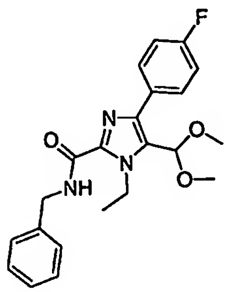
5-Dimethoxymethyl-1-ethyl-4-(4-fluoro-phenyl)-1H-imidazole



A solution of dimethoxy-acetaldehyde (2.2 mL, 8.6 mmol, 45% in methyl-tert-butyl ether) and ethylamine (10.4 mL, 20.7 mmol) in anhydrous tetrahydrofuran (30 mL), under a nitrogen atmosphere, was stirred for approximately 3 hours at ambient temperature. α-(*p*-Toluenesulfonyl)-4-fluorobenzylisonitrile (2.0 g, 6.9 mmol) was added and the mixture was stirred for an additional 18 hours at ambient temperature. The resultant yellow slurry was concentrated *in vacuo* to 30% initial volume. Water (15 mL) was added and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with 1m sodium hydroxide solution (20 mL) and dried over anhydrous sodium sulfate. The solution was concentrated *in vacuo* to a crude oil which was purified by chromatography on silica (10 to 80% ethyl acetate in hexanes) to yield 1.13 g of the desired product as a light yellow oil. Low resolution mass spectroscopy (APCI) *m/z* 265 $[M + H]^+$.

Step B

5-Dimethoxymethyl-1-ethyl-4-(4-fluoro-phenyl)-1H-imidazole-2-carboxylic acid benzylamide



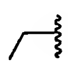
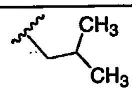
A stirred solution of 5-Dimethoxymethyl-1-ethyl-4-(4-fluoro-phenyl)-1H-imidazole (1.13 g., 4.3 mmol) in anhydrous tetrahydrofuran (15 mL), cooled to -78 °C, was treated with n-Butyllithium (3.2 mL, 6.3 mmol, 2.0 M in pentane) while maintaining the temperature below -70° C. After 30 minutes, the reaction mixture was treated with isocyanatomethyl-benzene (1.06 mL, 8.5 mmol) and allowed to warm to ambient temperature over 30 min. Saturated sodium bicarbonate solution (20 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL). The combined extracts were concentrated *in vacuo* to a yellow slurry which was triturated in 1-propanol. The fine white precipitate was removed by vacuum filtration washing with 1-propanol. The filtrate was concentrated *in vacuo* to a yellow oil. The oil was purified by chromatography on silica (10 to 60% ethyl acetate in hexanes) to yield 1.51 g of desired product as a light yellow oil. Low resolution mass spectroscopy (APCI) m/z 398 $[M + H]^+$.

Steps C-H were carried out in a similar manner as Example 1.

Compounds with variations on R^1 were made using a similar reaction scheme as shown in Ex. 4 and representative compounds are shown, along with characterizing data, in Table III.

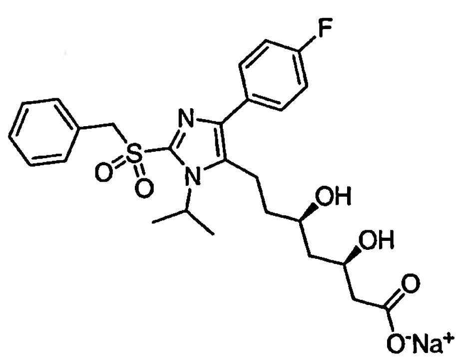
Variations On Example 4

TABLE III

R^1	MS	Theory			Found		
		C	H	N	C	H	N
	484	57.09	6.07	7.68	57.45	5.98	7.22
	498	58.10	6.45	7.53	58.26	6.13	7.13
	512	58.42	6.45	7.30	58.82	6.47	6.78

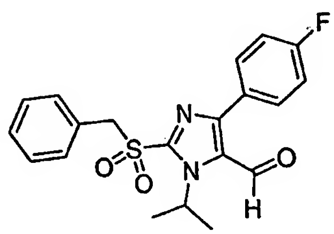
Example 5

(3R,5R)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazole-4-yl]-3,5-dihydroxy-heptanoic acid sodium salt.



Step A

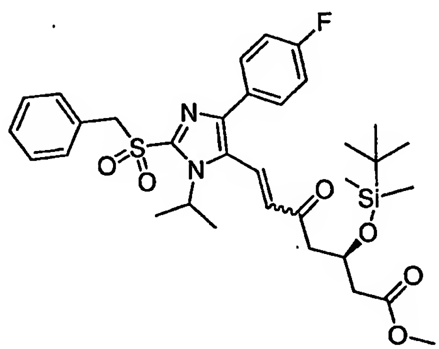
5-(4-Fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazole-4-carbaldehyde



A solution of 5-Dimethyoxymethyl-4-(4-fluoro-phenyl)-1-isopropyl-1*H*-imidazole (510 mg., 1.8 mmol) in anhydrous tetrahydrofuran (15 mL), cooled to -78 C (dry ice/acetone bath) under nitrogen, was treated with *n*-butyllithium (1.4 mL, 2.8 mmol, 2.0 M in pentane) dropwise via syringe while maintaining temperature below -70° C. The reaction mixture was stirred at –78 °C for 30 minutes, then treated with benzyl disulfide (1.15 g, 4.6 mmol) and stirred at –78 °C for 1 hour. The reaction mixture was removed from the cooling bath and allowed to warm to ambient temperature. After 2 hours, the reaction mixture was concentrated to 50% of its original volume under stream of dry nitrogen, then diluted with methylene chloride (10 mL), and treated with 3-chloro-benzenecarboperoxic acid (2.05 g, 9.15 mmol, 77%). The resulting mixture was stirred for 30 min. at ambient temperature, then treated with a second aliquot of 3-chloro-benzenecarboperoxic acid (2.05 g, 9.15 mmol, 77%) and stirred for 18 hours at ambient temperature. 3-chlorobenzoic acid was removed by filtration, and the filter cake was rinsed with chloroform (10 mL). The filtrate was treated with 3-chloro-benzenecarboperoxic acid (2.05 g, 9.15 mmol, 77%), stirred for 10 minutes at ambient temperature and filtered again. The filtrate was concentrated *in vacuo* and the crude material was partitioned between CH_2Cl_2 and 1M sodium hydroxide solution. The organic layer was removed, washed with brine, dried (Na_2SO_4), and concentrated to a yellow oil. Purification by flash chromatography (SiO_2, ethyl acetate/hexanes 1:9 to 6:4) provided the desired product as an amorphous powder. Low resolution mass spectroscopy (APCI) *m/z* 387 $[M + H]^+$.

Step B

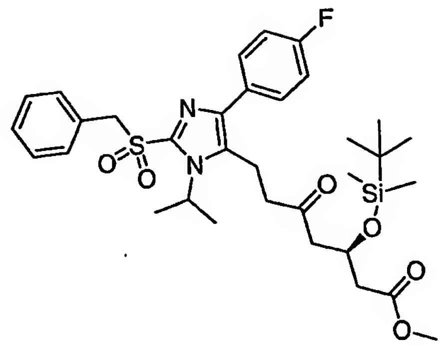
<u>(R)-3-(tert-Butyl-dimethyl-silanyloxy)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-5-oxo-hept-6-enoic acid methyl ester</u>



A solution of 5-(4-Fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazole-4-carbaldehyde (0.318 g., 0.82 mmol) and (R)-3-(tert-Butyl-dimethyl-silanyloxy)-5-oxo-6-(triphenyl-λ-5-phosphanylidene)-hexanoic acid methyl ester (0.66 g., 1.2 mmol) in toluene (5 mL) was heated to reflux for 24 hours under nitrogen atmosphere. The cooled reaction mixture was concentrated *in vacuo* to give an orange oil. Purification by flash chromatography (SiO_2, ethyl acetate/hexanes 3:17 to 1:1) provided the desired product as an red-orange glass; yield: 0.347 g; Low resolution mass spectroscopy (APCI) *m/z* 643 $[M + H]^+$.

Step C

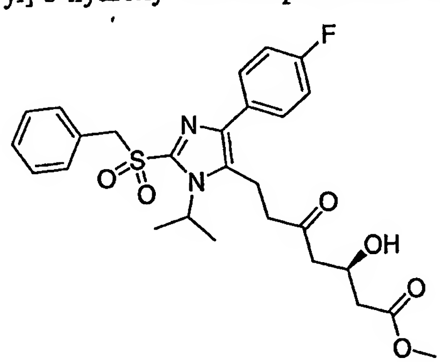
(R)-3-(tert-Butyl-dimethyl-silanyloxy)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-5-oxo-heptanoic acid methyl ester



A solution of (R)-3-(tert-Butyl-dimethyl-silanyloxy)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-5-oxo-hept-6-enoic acid methyl ester (374 mg, 0.54 mmol) in methanol – tetrahydrofuran (1:1) was hydrogenated over 5% $Pd/BaSO_4$ (0.2 g.) and hydrogen atmosphere (4295 psi per mol) for 39.1 hours. The reaction mixture was filtered through celite and concentrated *in vacuo* to give the desired product as a light yellow glass; yield 0.366 g; Low resolution mass spectroscopy (APCI) *m/z* 645 $[M + H]^+$. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm -0.0 (m, 3H) 0.1 (m, 3H) 0.8 (m, 9H) 1.3 (m, 6H) 1.4 (s, 1H) 2.5 (d, *J*=6.1 Hz, 2H) 2.6 (m, 3H) 3.1 (t, *J*=8.1 Hz, 2H) 3.7 (m, 3H) 4.5 (m, 1H) 4.8 (d, *J*=9.0 Hz, 2H) 5.0 (s, 1H) 7.1 (ddd, *J*=8.7, 6.7, 2.2 Hz, 2H) 7.3 (m, 5H) 7.6 (m, 2H)

Step D

(R)-7-[5-(4-Fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-3-hydroxy-5-oxo-heptanoic acid methyl ester

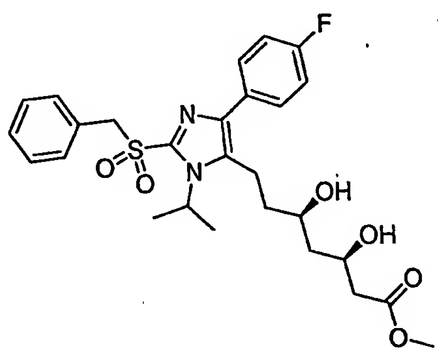


An ice cold solution of (R)-3-(tert-Butyl-dimethyl-silanyloxy)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-5-oxo-heptanoic

acid methyl ester (0.366 g., 0.57 mmol) in tetrahydrofuran (10 mL) in 50 mL conical polypropylene tube was treated with hydrogen fluoride-pyridine (3 mL, 70). The resulting mixture was warmed to ambient temperature and stirred for 1 hour. The reaction mixture was treated with 1M sodium carbonate solution (40 mL, pH = 11), diluted with water, and extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with saturated sodium bicarbonate solution, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude product as an orange glass; yield: 0.290 g; Low resolution mass spectroscopy (APCI) *m/z* 531 $[M + H]^+$.

Step E

(3R,5R)-7-[5-(4-Fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid methyl ester



A solution of (R)-7-[5-(4-Fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-3-hydroxy-5-oxo-heptanoic acid methyl ester (290 mg., 0.547 mmol) in anhydrous tetrahydrofuran (10 mL) was cooled to –78 °C (dry ice – acetone bath) under nitrogen atmosphere and treated with diethylmethoxyborane (0.222 mL, 1.64 mmol) The reaction mixture was stirred for 30 minutes at -78° C, then treated with solid sodium borohydride (29 mg., 0.77 mmol, Aldrich Chemical Co.). Stirring was continued flor 2 hours at –78 °C. The reaction mixture was quenched with glacial acetic acid (6 drops), warmed to 0 °C, and treated with 2-aminoethanol (0.198 mL, 3.28 mmol). After stirring for 30 minutes at ambient temperature, the reaction mixture was made basic (pH 11) with saturated sodium

bicarbonate solution (20 mL), dilted with water and extracted dichloromethane. The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated to a crude glass. Purification by flash chromatography (SiO_2, ethyl acetate/hexanes 1:4 to 3:2) provided the desired product as an light yellow glass; yield: 0.151 g; Low resolution mass spectroscopy (APCI) *m/z* 533 $[M + H]^+$. ^1H NMR (400 MHz, CHLOROFORM-D) δppm 0.9 (m, 3H) 1.3 (m, 1H) 1.4 (m, 5H) 1.5 (m, 1H) 1.7 (m, 1H) 1.9 (m, 1H) 2.4 (dd, *J*=15.6, 6.6 Hz, 1H) 2.6 (dd, *J*=15.6, 6.6 Hz, 1H) 2.9 (m, 1H) 3.2 (m, 1H) 3.7 (m, 3H) 3.9 (m, 1H) 4.3 (m, 1H) 4.8 (m, 2H) 5.0 (m, 1H) 7.1 (m, 2H) 7.3 (m, 5H) 7.6 (m, 2H)

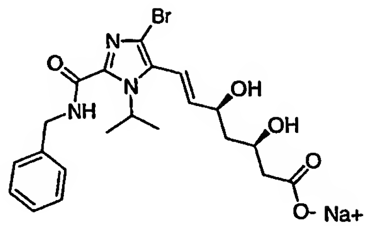
Step F

(3R,5R)-7-[5-(4-fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazole-4-yl]-3,5-dihydroxy-heptanoic acid sodium salt.

A solution of (3R,5R)-7-[5-(4-Fluoro-phenyl)-3-isopropyl-2-phenylmethanesulfonyl-3H-imidazol-4-yl]-3,5-dihydroxy-heptanoic acid methyl ester (151 mg., 0.284 mmol) in tetrahydrofuran-water (2 mL, 1:1) was treated with aqueous sodium hydroxide (0.269 mL, 1 M). The resulting mixture was stirred for 2 hours at ambient temperature. The reaction mixture was diluted with water (20 mL) and lyophilized to give the desired product as a fluffy light yellow powder; yield 0.138 g; Low resolution mass spectroscopy (APCI) *m/z* 519 $[M + H]^+$. CHN Combustion Analysis: Theoretical : C = 54.38%, H = 5.92%, N = 4.88% Found: C = 53.99%, H = 5.83%, N = 4.67%

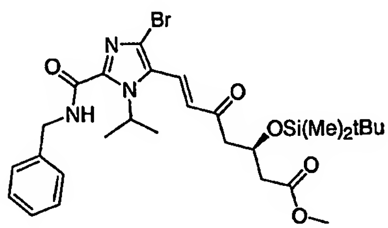
Example 6

(3*R*,5*S*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3,5-dihydroxy-hept-6-enoic acid sodium salt



Step A

(3R)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-hept-6-enoic acid methyl ester



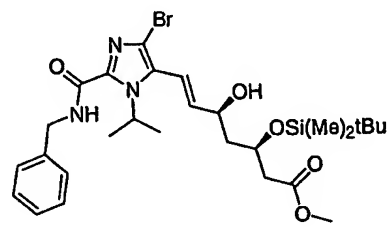
Preparation:

A solution of 4-bromo-5-formyl-1-isopropyl-1H-imidazole-2-carboxylic acid benzylamide (632 mg, 1.80 mmol) and *(3R)*-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-6-(triphenyl-15-phosphanylidene)-hexanoic acid methyl ester (1.18 g, 2.21 mmol) in toluene (8 mL) was heated at reflux for 19 h. The reaction mixture was concentrated in vacuo. Chromatography on silica gel [gradient elution, dichlormethane to dichloromethane-methanol (9:1)] afforded 299 mg of the product plus an additional batch of impure material. Re-purification of the latter afforded an additional 170 mg (43% total yield) of *(3R)*-7-(2-benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-hept-6-enoic acid methyl ester as a brown film: ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (br t, J = 6.0 Hz, 1 H), 7.60 (d, J = 15.9 Hz, 1 H), 7.38-7.27 (m, 5 H), 7.15 (d, J = 15.9 Hz, 1 H), 6.19 (m, 1 H), 4.69 (m, 1 H), 4.55 (d, J = 6.1 Hz, 2 H), 3.68 (s, 3 H), 2.90 (m, 2 H), 2.58 (m, 2 H), 1.59 (dd, J = 7.1, 2.0 Hz, 6 H), 0.83 (s, 9 H),

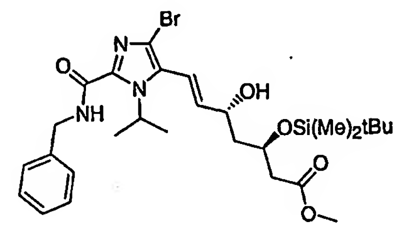
0.08 (s, 3 H), 0.05 (s, 3 H). MS(APCI+) found for $C_{28}H_{40}BrN_3O_5Si$: *m/z* 606.2, 608.2 $[M+H]^+$.

Step B

(3*R*,5*S*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-hydroxy-hept-6-enoic acid methyl ester and (3*R*,5*R*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-hydroxy-hept-6-enoic acid methyl ester



and



Preparation:

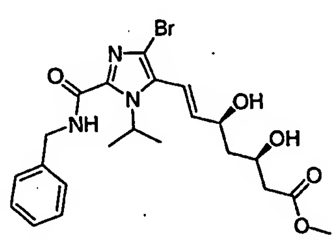
A solution of *(3R)*-7-(2-benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-oxo-hept-6-enoic acid methyl ester in methanol (7 mL) was cooled to –78 °C and treated with sodium borohydride (30 mg, 0.79 mmol). The resultant reaction mixture was stirred 45 min at –78 °C. An additional portion of sodium borohydride (20 mg, 0.53 mmol) was added and the reaction mixture was stirred an additional 45 min at –78 °C. The reaction mixture was quenched with water (1 mL), diluted with ethyl acetate (40 mL) and warmed to ambient temperature. The organic layer was washed with water and saturated brine, dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel [gradient elution, dichloromethane to dichloromethane-ether (19:1)] afforded a forerun of recovered starting material (40 mg) and then the faster-moving *anti* alcohol (3*R*,5*R*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-hydroxy-hept-6-enoic acid methyl ester (16 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (br t, J = 5.9 Hz, 1 H), 7.38-7.27 (m, 5 H), 6.57 (dd, J = 15.9, 1.7 Hz, 1 H), 6.39 (dd, J = 15.9, 4.6 Hz, 1 H), 6.01 (m, 1 H), 4.63 (m, 1 H), 4.54 (d, J = 6.1 Hz, 2 H), 4.52 (m, 1 H), 3.69 (s,

3 H), 3.35 (br s, 1 H), 2.66 (m, 2H), 1.85 (m, 2 H), 1.54 (dd, J = 6.9, 0.9 Hz, 6 H), 0.90 (s, 9 H), 0.15 (s, 3 H), 0.11 (s, 3 H). MS(APCI+) found for $C_{28}H_{42}BrN_3O_5Si$: *m/z* 608.2, 610.2 $[M+H]^+$.

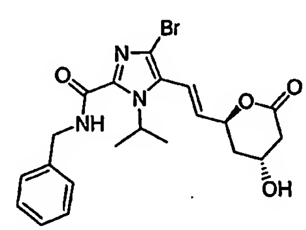
Further elution with dichloromethane-ether (19:1) afforded fractions containing both the *syn* and *anti* alcohols (112 mg). Last to elute was the pure fractions of the slower-moving *syn* alcohol (3*R*,5*S*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-hydroxy-hept-6-enoic acid methyl ester (28 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (br t, J = 6.0 Hz, 1 H), 7.36-7.27 (m, 5 H), 6.56 (dd, J = 15.9, 1.7 Hz, 1 H), 6.41 (dd, J = 15.9, 4.9 Hz, 1 H), 5.99 (br m, 1 H), 4.55 (m, 1 H), 4.45 (d, J = 6.1 Hz, 2 H), 4.41 (m ,1 H), 3.68 (s, 3 H), 3.08 (br d, J = 6.8 Hz, 1 H), 2.61 (m, 2 H), 1.92 (ddd, J = 14.4, 4.9, 3.2 Hz, 1 H), 1.80 (ddd, J = 14.4, 8.5, 7.3 Hz, 1 H), 1.54 (d, J = 6.8 Hz, 6 H), 0.91 (s, 9 H), 0.15 (s, 3 H), 0.12 (s, 3 H). MS(APCI+) found for $C_{28}H_{42}BrN_3O_5Si$: *m/z* 608.2, 610.2 $[M+H]^+$.

Step C

(3*R*,5*S*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3,5-dihydroxy-hept-6-enoic acid methyl ester and (3*R*,5*S*)-7-(2-benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3,5-dihydroxy-hept-6-enoic acid methyl ester and 4-Bromo-5-[*(2S, 4R)*-2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-vinyl]-1-isopropyl-1H-imidazole-2-carboxylic acid benzylamide



and



A solution of (3*R*,5*S*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3-(tert-butyl-dimethyl-silanyloxy)-5-hydroxy-hept-6-enoic acid methyl ester

(50 mg, 0.082 mmol) in tetrahydrofuran (5 mL) was cooled to 0 °C and treated with tetrabutylammonium fluoride (0.12 mL, 1.0 M in tetrahydrofuran). The reaction mixture was stirred 45 min at 0 °C. Saturated aqueous ammonium chloride solution (1 mL) was added and the reaction was partitioned between ethyl acetate-hexanes (1:1, 40 mL) and water (10 mL). The organic layer was washed with water (2 x 10 mL) and saturated brine (10 mL), dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel [gradient elution, dichloromethane to dichloromethane-methanol (9:1)] afforded a 2:1 mixture of (3*R*,5*S*)-7-(2-benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3,5-dihydroxy-hept-6-enoic acid methyl ester and 4-Bromo-5-[*(2S, 4R)*-2-(4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-vinyl]-1-isopropyl-1H-imidazole-2-carboxylic acid benzylamide (28 mg, 70% yield).

Step D

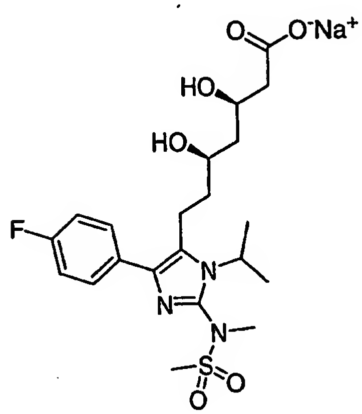
(3*R*,5*S*)-7-(2-Benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3,5-dihydroxy-hept-6-enoic acid sodium salt

The products of step C (28 mg, 0.058 mmol) were dissolved in tetrahydrofuran (1.0 mL) and water (1.0 mL). Aqueous sodium hydroxide (0.055 mL of a 1.0 M soloution) was added. The resultant reaction mixture was stirred 2 h at room temperature. The tetrahydrofuran was removed in vacuo and the remaining aqueous solution was frozen (-78 °C bath) and lyophilized under high vacuum to afford (3*R*,5*S*)-7-(2-benzylcarbamoyl-5-bromo-3-isopropyl-3H-imidazol-4-yl)-3,5-dihydroxy-hept-6-enoic acid
sodium salt (28.7 mg, 99% yield) as a fluffy white powder: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (br t, J = 6.2 Hz, 1 H), 7.32-7.18 (m, 5 H), 6.45 (d, J = 16.1 Hz, 1 H), 6.32 (dd, J = 16.1, 4.7 Hz, 1 H), 5.61 (m, 1 H), 5.31 (br s, 1 H), 4.37-4.30 (m, 3 H), 3.76 (m, 1 H), 2.02 (dd, J = 14.9, 3.8 Hz, 1 H), 1.82 (dd, J = 14.9, 8.2 Hz, 1 H), 1.56 (m, 1 H), 1.45 (m, 1 H), 1.42 (d, J = 7.0 Hz, 6 H). MS(APCI+) found for $C_{21}H_{25}BrN_3O_5Na$: *m/z* 480.0, 482.0 $[C_{21}H_{26}BrN_3O_5 + H]^+$. Anal.

Calcd/Found for $C_{21}H_{25}BrN_3O_5Na{\cdot}H_2O$: C, 48.47/48.66; H, 5.23/4.87; 8.08/7.76.

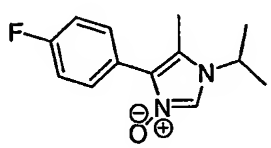
Example 7

(3R,5R)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxyheptanoate sodium salt



Step A

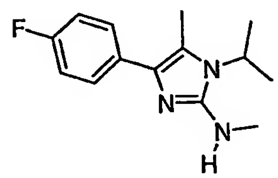
4-(4-Fluorophenyl)-1-isopropyl-5-methyl-1H-imidazole 3-oxide



A homogeneous mixture of 1-(4-fluorophenyl)-1,2-propanedione 1-oxime (44.3 g, 245 mmol, WO00/53585, PCT/US00/05241) and 1,3,5-triisopropyl hexahydro-sym-triazine (17.7 g, 83.2 mmol) in absolute ethanol (315 mL) was heated at reflux for 5 hrs under a nitrogen atmosphere, and the solvent was then removed in vacuo. The residue was triturated with diethyl ether (400 mL), and the solid product was removed by filtration and dried in vacuo to give 53.7 g (94%) of the title compound as a white solid: mp 153-156°C; MS (APCI$^+$) m/z 235.

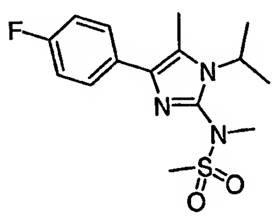
Step B

[4-(4-Fluorophenyl)-1-isopropyl-5-methyl-1H-imidazol-2-yl]methylamine



A stirred solution of 4-(4-fluorophenyl)-1-isopropyl-5-methyl-1H-imidazole 3-oxide from Step A (6.00 g, 25.6 mmol) in dry methylene chloride (50 mL) at 0°C under a nitrogen atmosphere was treated with a solution of methyl isothiocyanate (1.97 g, 26.9 mmol) in dry methylene chloride (20 mL) dropwise. The resulting homogeneous mixture was stirred at ambient temperature for 2 days and was then concentrated and dried in vacuo to give ~6.3 g (~99%, ~90% purity) of the title compound as an amber foam, MS (APCI$^+$) m/z 248, which was used in the next step without further purification.

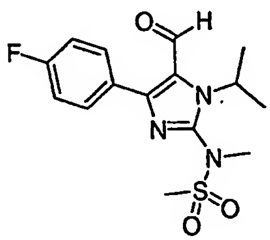
Step C :N-[4-(4-Fluorophenyl)-1-isopropyl-5-methyl-1H-imidazol-2-yl]-N-methyl-methanesulfonamide



A stirred solution of [4-(4-fluorophenyl)-1-isopropyl-5-methyl-1H-imidazol-2-yl]methylamine from Step B (4.00 g, 16.2 mmol) and triethylamine (3.38 mL, 24.3 mmol) in dry methylene chloride (50 mL) under a nitrogen atmosphere was cooled to –20°C and treated with a solution of methanesulfonyl chloride (1.31 mL, 17.0 mmol) in dry methylene chloride (15 mL) dropwise over 40 mins. The resulting mixture was stirred at –20°C for 4 hrs and was then diluted with methylene chloride (30 mL), washed with saturated aqueous sodium bicarbonate (50 mL) and brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (15-30% ethyl acetate in hexanes) to give 1.68 g (32%) of the title compound as a white solid: mp 98-101°C; MS (APCI$^+$) m/z 326.

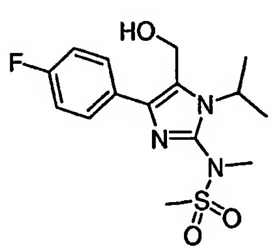
Step D

N-[4-(4-Fluorophenyl)-5-formyl-1-isopropyl-1H-imidazol-2-yl]-N-methyl-methanesulfonamide



A stirred solution of N-[4-(4-fluorophenyl)-1-isopropyl-5-methyl-1H-imidazol-2-yl]-N-methyl-methanesulfonamide from Step C (1.65 g, 5.07 mmol) in a mixture of tetrahydrofuran (50 mL), water (50 mL) and glacial acetic acid (13 mL) was treated with ceric ammonium nitrate (11.3 g, 20.6 mmol) portionwise over 15 mins. The resulting pale yellow homogeneous mixture was stirred at ambient temperature for 2 hrs and was then added to ice water (200 mL) with vigorous stirring. The mixture was extracted with methylene chloride (200 mL), and the organic phase was washed carefully with saturated aqueous sodium bicarbonate (100 mL) and brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (15-25% ethyl acetate in hexanes) to give 1.06 g (65%) of the title compound as a white solid: mp 119-123°C; MS ($APCI^+$) m/z 340.

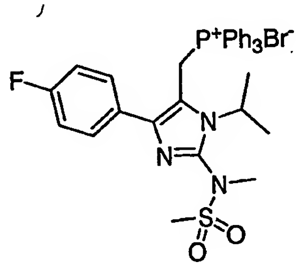
Step E:N-[4-(4-Fluorophenyl)-5-hydroxymethyl-1-isopropyl-1H-imidazol-2-yl]-N-methyl-methanesulfonamide



A stirred solution of N-[4-(4-fluorophenyl)-5-formyl-1-isopropyl-1H-imidazol-2-yl]-N-methyl-methanesulfonamide from Step D (0.865 g, 2.55 mmol) in dry tetrahydrofuran (25 mL) under a nitrogen atmosphere was cooled in an ice-salt

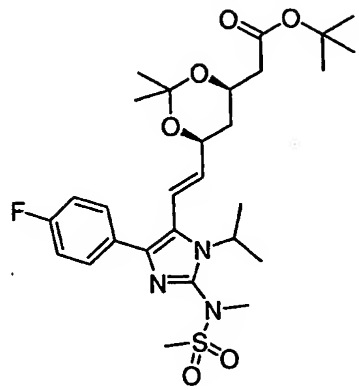
bath and treated with lithium tri-tert-butoxyaluminohydride (1M in tetrahydrofuran, 3.82 mL) dropwise over 5 mins. The resulting homogeneous mixture was stirred at -5-0°C for 1.5 hrs and was then quenched slowly with saturated aqueous ammonium chloride (10 mL). The resulting heterogeneous mixture was diluted with 1M hydrochloric acid (25 mL) and ethyl acetate (50 mL) and stirred for ~10 mins to allow the solids to dissolve, and then the layers were separated. The aqueous phase was extracted with ethyl acetate (50 mL), and the combined organic phase was washed with brine (50 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (1-5% methanol in dichloromethane) to give 0.86 g (94%) of the title compound as a white solid: mp 173-174°C; MS (APCI$^+$) m/z 342.

Step F:[5-(4-Fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-ylmethyl]triphenylphosphonium bromide



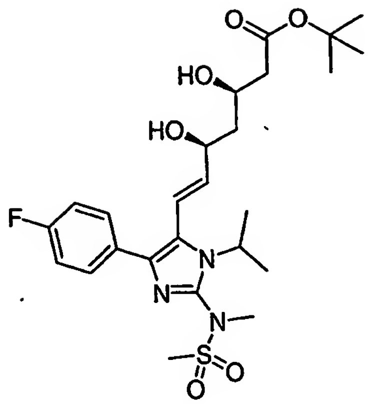
To a stirred solution of N-[4-(4-fluorophenyl)-5-hydroxymethyl-1-isopropyl-1H-imidazol-2-yl]-N-methyl-methanesulfonamide from Step E (0.855 g, 2.50 mmol) in dry acetonitrile (50 mL) under nitrogen was added triphenylphosphine hydrobromide (0.857 g, 2.50 mmol). The resulting homogeneous mixture was placed in a 65°C heating bath and stirred at this temperature for 2 days. The heating bath was removed, and the mixture was stirred at ambient temperature over the weekend and then concentrated in vacuo to give 1.67 g (95%, ~90% purity) of the title compound as an off-white amorphous solid, MS (APCI$^+$) m/z 586, which was used without further purification.

Step G:((4R,6S)-6-{2-[5-(4-Fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-vinyl}-2,2-dimethyl-[1,3]dioxan-4-yl)acetic acid tert-butyl ester



A solution of [5-(4-fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-ylmethyl]triphenylphosphonium bromide from step F (1.34 g, 2.01 mmol) in dry dimethylsulfoxide (9 mL) and tetrahydrofuran (45 mL) under a nitrogen atmosphere was cooled to -78^{o}C, affording a white slurry, and treated with sodium bis(trimethylsilyl)amide (1M in tetrahydrofuran, 2.41 mL) dropwise over ~2 min with vigorous stirring. The resulting yellow slurry was stirred at -78^{o}C for 7-8 mins and was then treated with a solution of ((4R,6S)-6-formyl-2,2-dimethyl-[1,3]dioxan-4-yl)acetic acid tert-butyl ester (0.779 g, 3.02 mmol, Syn. Comm. 2003, 33(13), 2275-83, alternate name tert-butyl (3R,5S)-6-oxo-3,5-O-isopropylidene-3,5-dihydroxyhexanoate) in dry tetrahydrofuran (2.2 mL) dropwise over 2 mins. The mixture was stirred at -78^{o}C for 30 mins, the cooling bath was removed and the mixture was allowed to warm to ambient temperature and stir for 3 hrs. The mixture was then quenched slowly with saturated aqueous ammonium chloride (10 mL) and partitioned between water (20 mL) and ethyl acetate (20 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo, and the residue was purified by silica gel chromatography (20-30% ethyl acetate in hexanes) to give 0.73 g of the title compound (~4:1 mixture of cis/trans alkene isomers) as a white amorphous solid. The product mixture was used as is in the next step. MS (APCI$^+$) m/z 566.

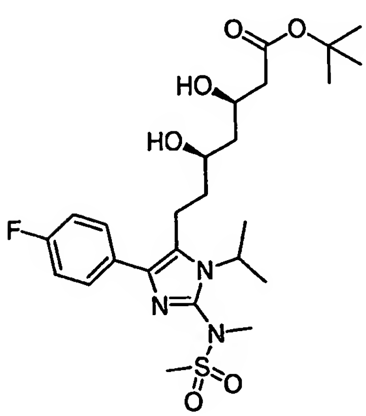
Step H:(3R,5S)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxyhept-6-enoic acid tert-butyl ester



A solution of ((4R,6S)-6-{2-[5-(4-fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-vinyl}-2,2-dimethyl-[1,3]dioxan-4-yl)acetic acid tert-butyl ester from Step G (0.335 g, 0.592 mmol) in methanol (24 mL) was treated with 1N hydrochloric acid (1.48 mL), and the mixture was stirred at ambient temperature overnight. The solvent was then removed in vacuo, the residue was diluted with water (20 mL) and ethyl acetate (25 mL) and the layers were separated. The organic phase was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo, and the residue was purified by silica gel chromatography (50% ethyl acetate in hexanes) to give 247 mg (79%) of the title compound (mixture of cis/trans alkene isomers) as a white amorphous solid: MS (APCI$^+$) m/z 526.

Step I

(3R,5R)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxyheptanoic acid tert-butyl ester



A solution of (3R,5S)-7-[5-(4-fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxyhept-6-enoic acid tert-butyl ester from Step H (0.449 g, 0.854 mmol) in methanol (16 mL) was treated with 10% palladium-on-carbon (0.10 g), and the mixture was shaken on a Parr apparatus under a hydrogen atmosphere (50 psi) for 1.75 hrs. The mixture was then filtered through Celite to remove the catalyst, the filtrate was concentrated in vacuo, and the residue was purified by silica gel chromatography (50% ethyl acetate/hexanes) to give 301 mg (67%) of the title compound as a white amorphous solid: MS (APCI$^+$) m/z 528.

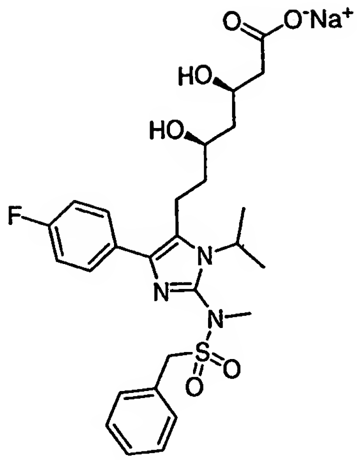
Step J

(3R,5R)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxyheptanoate sodium salt

A solution of (3R,5R)-7-[5-(4-fluorophenyl)-3-isopropyl-2-(methanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxyheptanoic acid tert-butyl ester from Step I (0.250 g, 0.474 mmol) in methanol (15 mL) was treated with aqueous sodium hydroxide (1.028N, 0.495 mL), and the reaction mixture was stirred at ambient temperature for 26 hrs. The solvent was then removed in vacuo, and the residue was taken up in a minimum of 10% methanol in dichloromethane (~3 mL), diluted with additional methylene chloride (10 mL) and filtered to remove any residual sodium hydroxide. The filtrate was concentrated in vacuo, the residue was triturated with diethyl ether (~20 mL) and the solid was collected by filtration and dried in vacuo to give 220 mg (94%) of the title compound as a white amorphous solid: NMR (400 MHz, DMSO-d_6) □7.60, 7.47, 7.14, 4.92, 4.51, 3.73, 3.65, 3.24, 3.10, 2.90, 2.70, 1.99, 1.78, 1.60, 1.45, 1.32; MS (APCI$^-$) m/z 470.

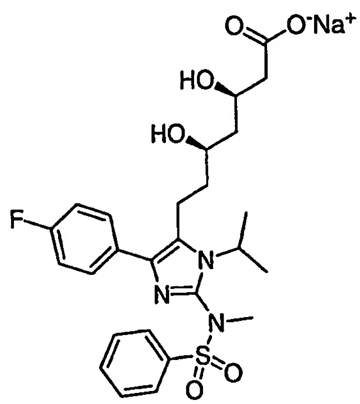
Example 8

(3R,5R)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-(phenylmethanesulfonyl-methyl-amino)-3H-imidazol-4-yl]-3,5-dihydroxyheptanoate sodium salt



The title compound was prepared by a method analogous to that described in Steps C to J of Example 7, substituting benzylsulfonyl chloride for methanesulfonyl chloride in Step C. MS (APCI^{+}) m/z 548; mp 191-194°C (dec.).

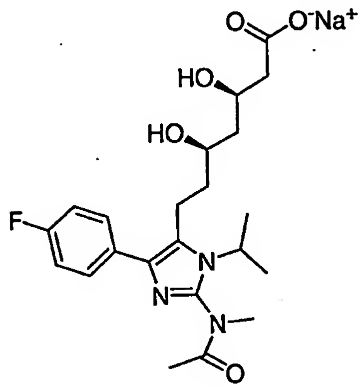
Example 9
(3R,5R)-7-[2-(Benzenesulfonyl-methyl-amino)-5-(4-fluorophenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxyheptanoate sodium salt



The title compound was prepared by a method analogous to that described in Steps C to J of Example 7 substituting benzenesulfonyl chloride for methanesulfonyl chloride in Step C. NMR (400 MHz, DMSO-d_6) δ 7.87, 7.73, 7.63, 7.51, 7.12, 4.93, 4.59, 3.73, 3.68, 2.94, 2.72, 1.98, 1.79, 1.62, 1.50, 1.43, 1.32; MS (APCI^{-}) m/z 532.

Example 10

(3R,5R)-7-[2-(Acetyl-methyl-amino)-5-(4-fluorophenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxyheptanoate sodium salt

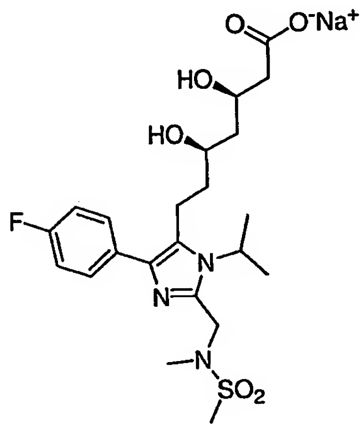


A stirred solution of [4-(4-fluorophenyl)-1-isopropyl-5-methyl-1H-imidazol-2-yl]methylamine from Step B of Example 7 (3.10 g, 12.5 mmol) and pyridine (2.03 mL, 25.1 mmol) in dry methylene chloride (50 mL) under a nitrogen atmosphere was treated with acetic anhydride (1.42 mL, 15.0 mmol). The resulting mixture was stirred at ambient temperature over the weekend and was then diluted with methylene chloride (50 mL), washed with saturated aqueous sodium bicarbonate (50 mL) and brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (30-80% ethyl acetate in hexanes) to give 1.16 g (32%, ~80% purity) of N-[4-(4-fluorophenyl)-1-isopropyl-5-methyl-1H-imidazol-2-yl]-N-methyl-acetamide as an amber amorphous solid which was used without further purification. An analytical sample was prepared by radial chromatography (4% methanol in dichloromethane; 2000 micron silica gel rotor) to give a white solid: mp 108-111°C; MS (APCI^{+}) m/z 290.

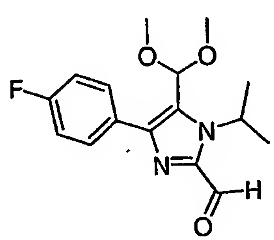
The remaining steps were carried out in a similar manner as Steps D to J of Example 7 to give the title compound as a white solid: NMR (400 MHz, DMSO-d_6) □7.60, 7.52, 7.13, 4.92, 4.37, 3.73, 3.65, 3.00, 2.95, 2.75, 1.99, 1.78, 1.70, 1.62, 1.45, 1.32; MS (APCI^{-}) m/z 434.

Example 11

(3R,5R)-7-{5-(4-Fluorophenyl)-3-isopropyl-2-[(methanesulfonyl-methyl-amino)-methyl]-3H-imidazol-4-yl}-3,5-dihydroxyheptanoate sodium salt



Step A
5-Dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazole-2-carboxaldehyde

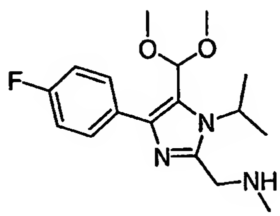


A stirred solution of lithium diisopropylamide (1.5M in cyclohexane, 9.67 mL, 14.5 mmol) in dry tetrahydrofuran (43 mL) at –78°C under a nitrogen atmosphere was treated with a solution of 5-dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazole from Step A of Example 1 (3.67 g, 13.2 mmol) in dry tetrahydrofuran (10 mL) dropwise over 8 mins. The resulting mixture was stirred at -78°C for 25 mins and was then treated with N,N-dimethylformamide (4.08 mL, 52.7 mmol). After stirring for an additional 30 mins at -78°C, this mixture was allowed to warm to ambient temperature, at which point it was quenched with saturated aqueous ammonium chloride (25 mL) and diluted with ethyl acetate (50 mL) and water (25 mL). The layers were separated, and the organic phase was washed with water (50 mL) and brine (20 mL), dried over anhydrous Na_2SO_4 and

concentrated in vacuo. The residue was purified by silica gel chromatography (25% ethyl acetate in hexanes) to give 3.41 g (84%) of the title compound as a white solid: mp 98-99°C; MS (APCI$^+$) m/z 307.

Step B

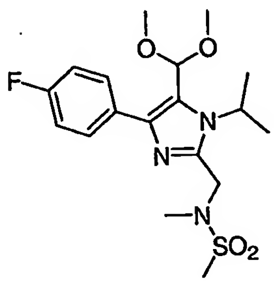
[5-Dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazol-2-ylmethyl]-methyl-amine



A stirred solution of 5-dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazole-2-carboxaldehyde from Step A (2.90 g, 9.47 mmol) in methanol (20 mL) at 0°C under a nitrogen atmosphere was treated with methylamine (2M in methanol, 28.4 mL) dropwise, stirred for 20 mins at 0°C, and then treated with sodium borohydride (0.716 g, 18.9 mmol) portionwise over 15 mins. The resulting homogeneous mixture was stirred at 0°C for 15 mins and at ambient temperature for 2.5 hrs, and then the solvent was removed in vacuo. The residue was diluted up with dichloromethane (150 mL), and this slurry was added slowly to ice-cold saturated aqueous sodium bicarbonate with vigorous stirring. This biphasic mixture was stirred until gas evolution ceased, the layers were separated, and the organic phase was washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a quantitative yield of the title compound as an opaque viscous oil, MS (APCI$^+$) m/z 322, which was used without further purification.

Step C

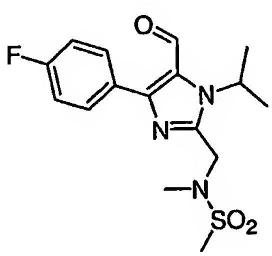
N-[5-Dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazol-2-ylmethyl]-N-methyl-methanesulfonamide



A stirred solution of [5-dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazol-2-ylmethyl]-methyl-amine from Step B (1.36 g, 4.23 mmol) and triethylamine (0.885 mL, 6.35 mmol) in dry methylene chloride (42 mL) under a nitrogen atmosphere was cooled to 0°C and treated with methanesulfonyl chloride (0.36 mL, 4.65 mmol) dropwise. The resulting mixture was stirred at 0°C for 1.5 hrs and was then diluted with methylene chloride (20 mL), washed with saturated aqueous sodium bicarbonate (30 mL) and brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel chromatography (40-80% ethyl acetate in hexanes) to give an 80% yield of the title compound as a white solid: mp 136-138°C; MS (APCI$^+$) m/z 400.

Step D

N-[4-(4-Fluorophenyl)-5-formyl-1-isopropyl-1H-imidazol-2-ylmethyl]-N-methyl-methanesulfonamide



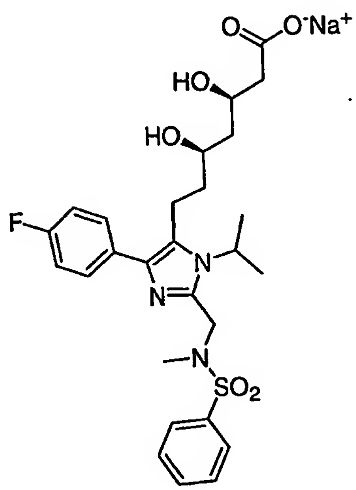
A stirred solution of N-[5-dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazol-2-ylmethyl]-N-methyl-methanesulfonamide from Step C (1.28 g, 3.20 mmol) in dry dichloromethane (5 mL) under a nitrogen atmosphere was treated with trifluoroacetic acid (7.5 mL), stirred for 1 hr at ambient temperature, and concentrated in vacuo. The residue was diluted up with 1M aqueous sodium hydroxide (50 mL) and extracted with dichloromethane (2 x 50 mL), and the

combined organic phase was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give 1.11 g (98%) of the title compound as a white solid: MS (APCI$^+$) m/z 354.

The remaining steps were carried out in a similar manner as Steps E to J of Example 7 to give (3R,5R)-7-{5-(4-fluorophenyl)-3-isopropyl-2-[(methanesulfonyl-methyl-amino)-methyl]-3H-imidazol-4-yl}-3,5-dihydroxyheptanoate sodium salt as a white solid: mp 177-180°C; MS (APCI$^-$) m/z 484.

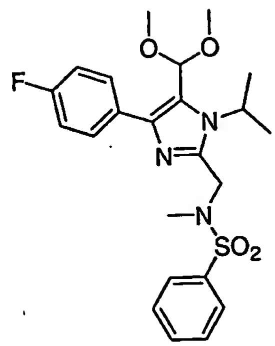
Example 12

(3R,5R)-7-[2-[(Benzenesulfonyl-methyl-amino)-methyl]-5-(4-fluorophenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxyheptanoate sodium salt



Step A

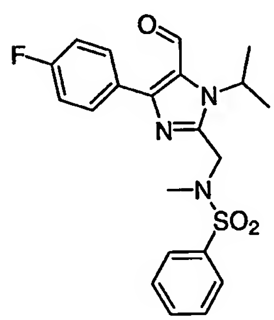
N-[5-Dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazol-2-ylmethyl]-N-methyl-benzenesulfonamide



The title compound was prepared by a method analogous to that described in Step C of Example 11, substituting benzenesulfonyl chloride for methanesulfonyl chloride. Mp 112-113°C; MS (APCI$^+$) m/z 462.

Step B

N-[4-(4-Fluorophenyl)-5-formyl-1-isopropyl-1H-imidazol-2-ylmethyl]-N-methyl-benzenesulfonamide



The title compound was prepared by a method analogous to that described in Step D of Example 11, substituting N-[5-dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazol-2-ylmethyl]-N-methyl-benzenesulfonamide for N-[5-dimethoxymethyl-4-(4-fluorophenyl)-1-isopropyl-1H-imidazol-2-ylmethyl]-N-methyl-methanesulfonamide. MS (APCI$^+$) m/z 416.

The remaining steps were carried out in a similar manner as Steps E to J of Example 7 to give (3R,5R)-7-[2-[(benzenesulfonyl-methyl-amino)-methyl]-5-(4-fluorophenyl)-3-isopropyl-3H-imidazol-4-yl]-3,5-dihydroxyheptanoate sodium salt as a white amorphous solid: NMR (400 MHz, DMSO-d_6) □7.87, 7.73, 7.63,

7.51, 7.12, 4.93, 4.59, 3.73, 3.68, 2.94, 2.72, 1.99, 1.79, 1.62, 1.51, 1.44, 1.32; MS (APCI) m/z 546.

FORMULATIONS

The compounds of the present invention including those exemplified herein and all compounds of Formula I, hereafter referred to as "compound(s)" can be administered alone or in combination with one or more therapeutic agents. These include, for example, other agents for treating, preventing or controlling dyslipidemia, non-insulin dependent diabetes mellitus, obesity, hyperglycemia, hypercholesteremia, hyperlipidemia, atherosclerosis, hypertriglyceridemia, or hyperinsulinemia.

The compounds are thus well suited to formulation for convenient administration to mammals for the prevention and treatment of such disorders.

The following examples further illustrate typical formulations of the compounds provided by the invention.

Formulation 1

Ingredient	Amount
compound	0.5 to 800 mg
sodium benzoate	5 mg
isotonic saline	1000 mL

The above ingredients are mixed and dissolved in the saline for IV administration to a patient.

Formulation 2

Ingredient	Amount
compound	0.5 to 800 mg
cellulose, microcrystalline	400 mg
stearic acid	5 mg
silicon dioxide	10 mg
sugar, confectionery	50 mg

The ingredients are blended to uniformity and pressed into a tablet that is well

suited for oral administration to a patient.

Formulation 3

Ingredient	Amount
compound	0.5 to 800 mg
starch, dried	250 mg
magnesium stearate	10 mg

The ingredients are combined and milled to afford material suitable for filling hard gelatin capsules administered to a patient.

Formulation 4

Ingredient	Amount % wt./(total wt.)
compound	1 to 50
Polyethylene glycol 1000	32 to 75
Polyethylene glycol 4000	16 to 25

The ingredients are combined via melting and then poured into molds containing 2.5 g total weight.

While embodiments of the invention have been illustrated and described, it is not intended that these embodiments illustrate and describe all possible forms of the invention. Rather, the words used in the specification are words of description rather than limitation, and it is understood that various changes may be made without departing from the spirit and scope of the invention.

BIOLOGICAL ASSAYS

The compounds of the invention have demonstrated HMG Co-A reductase inhibition in standard assays commonly employed by those skilled in the art. (See, e.g., J. of Lipid Research 1998; 39:75-84; Analytical Biochemistry, 1991; 196:211-214; RR 740-01077 Pharmacology 8-Nov-82) Accordingly, such compounds and formulations comprising such compounds are useful for treating, controlling or preventing *inter alia* hypercholesterolemia, hyperlipidemia, hypertriglyceridemia or atherosclerosis.

A.) *In Vitro* assay

Rat Liver Microsomal Isolation Procedure:

Male Charles River Sprague-Dawley rats were fed with 2.5% cholestyramine in rat chow diets for 5 days before sacrificing. Livers were minced and homogenized in a sucrose homogenizing solution in an ice bath 10 times. Homogenates were diluted into a final volume of 200 mL, and centrifuged 15 min. with a Sorvall Centrifuge at 5°C, 10,000 rpm (12,000 x G). The upper fat layer was removed and the supernatant decanted into fresh tubes. This step was repeated one more time before transferring the supernatant into ultracentrifuge tubes and centrifuged at 36,000 rpm (105,000 x G) for an hour at 5°C. The resulting supernatant was discarded and the pellet was added to total of 15 mL 0.2 M KH_2PO_4. Pellets were homogenized gently by hand about 10 times. Samples were pooled and diluted into total of 60 mL buffer. The protein concentration of the homogenate was determined by the Lowry Method using a BCA (Bicinchoninic acid), kit from Pierce Chemical Company. 1 mL aliquots of microsomes were kept frozen in liquid nitrogen.

HMGCoA (3-Hydroxy-3-methylglutaryl CoA) Reductase Assay:

Materials and Methods:

[3-^{14}C]-HMGCoA (57.0 mCi/mmol) was purchased from Amersham Biosciences, UK. HMGCoA, mevalonolactone, β-NADPH (β-Nicotinamide Adenine Dinucleotide Phosphate, Reduced form) were purchased from Sigma Chemical Co. AG 1-8X resin was purchased from Bio-Rad Laboratory.

One μL of dimethyl sulfoxide (DMSO) or 1 μL of DMSO containing a test compound at a concentration sufficient to give a final assay concentration of between 0.1 nM to 1 mM was placed into each well of a Corning 96 well plate. A Volume of 34 μL of buffer (100 mM NaH_2PO_4, 10 mM Imidazole and 10 mM EDTA), (Ethylenediaminetetra acetic acid) containing with 50 μg/mL rat liver microsomes was added into each well. After incubation for 30 min. on ice, 15 μL of ^{14}C-HMGCoA (0.024 μCi) with 15 mM NADPH , 25 mM DTT, (Dithiothreitol) was added and incubated at 37°C for an additional 45 min. The reaction was terminated by the addition of 10 μL of HCl followed by 5 μL of mevalonolactone. Plates were incubated at room temperature overnight to allow lactonization of mevalonate to mevalonolactone. The incubated samples were applied to columns containing 300 μL of AG1-X8 anion exchange resin in a Corning filter plate. The eluates were collected into Corning 96 well capture plates. Scintillation cocktail (Ultima-Flo-M) was added into each well and plates counted on a Trilux Microbeta Counter. The IC_{50} values were calculated with GraphPad software (Prism).

Procedure:

1. Add 1 μL DMSO or compounds into the wells according to the protocol
2. Add 35 μL incubation buffer with the rat microsomes into each well. Incubate 30 min. at 4°C
3. Add 15 μL ^{14}C-HMGCoA. Incubate 45 min. at 37°C
4. Add 10 μL HCl stop reagent
5. Add 5 μL mevelonolactone. Incubate overnight at room temperature
6. Apply the containing into the AG 1-X8 anion exchange resin in Corning filter plate

7. Collect the eluate into Corning capture plate
8. Add scintillation cocktail Ultima-Flo-M
9. Count on a Trilux Microbeta Counter
10. Calculate IC_{50} values

Compounds of the invention exhibit a range of IC_{50} values of less than about 500 nM. Preferred compounds of the invention exhibit a range of IC_{50} values of less than about 100 nM. More preferred compounds of the invention exhibit a range of IC_{50} values of less than about 20 nM. See, for example the compounds of Example 1, which has an IC_{50} of 9.75 nM, Example 7 which has an IC_{50} of 6.6 nM, and the first entry in Table I, which has an IC_{50} of 3.6 nM.

B.) Cell Assay

Protocol for Sterol Biosynthesis in Rat Hepatocytes:

Cell culture, compounds treatment and cell labeling:

Frozen rat hepatocytes purchased from XenoTech(cat# N400572) were seeded on 6-well collagen I coated plates at a density of 10^5 cells/per well. The cells were grown in DMEM, (Dulbecco's Modified Eagle Medium) (Gibco, #11054-020) containing 10% FBS (Fetal Bovine Serum) and 10 mM HEPES, (N-2-hydroxyethyl-piperazine-N^1-2-ethane sulfonic acid) (Gibco # 15630-080) for 24 hrs. The cells were pre-incubated with compounds for 4 hrs and then labeled by incubating in medium containing 1 uCi/per mL of ^{14}C acetic acid for an additional 4 hrs. After labeling, the cells were washed twice with 5 mM MOPS, (3-[N-morpholino]propane sulfonic acid) solution containing 150 mM NaCl and 1 mM EDTA and collected in the lysis buffer containing 10% KOH and 80%(vol.) ethanol.

Cholesterol extraction and data analysis:

In order to separate labeled cholesterol from labeled non-cholesterol lipids, the cells lysates were subject to saponification at 60°C for 2 hrs. The lysates were then combined with 0.5 volume of H_2O and 2 volumes of hexane, followed by 30 minutes of vigorous shaking. After the separation of two phases, the upper-phase solution was collected and combined with 5 volumes of scintillation cocktail. The

amount of ^{14}C cholesterol was quantified by liquid scintillation counting. The IC_{50} values were calculated with GraphPad software (Prism 3.03).

Compounds of the invention exhibit a range of IC_{50} values of less than about 1000 nM. Preferred compounds of the invention exhibit a range of IC_{50} values of less than about 100 nM. See, for example the compounds of Example 1, which has an IC_{50} of 0.73 nM, Example 7, which has an IC_{50} of 0.99 nM, and the first entry in Table I , which has an IC_{50} of 0.71 nM.

C.) Protocol for Sterol Biosynthesis in L6 Rat Myoblast:

Cell culture, compounds treatment and cell labeling:

L6 rat myoblast purchased from ATCC (CRL-1458) were grown in T-150 vented culture flasks and seeded on 12-well culture plates at a density of 60,000 cells per well. The cells were grown in DMEM, (Dulbecco's Modified Eagle Medium) (Gibco, #10567-014) containing 10% heat inactivated FBS (Fetal Bovine Serum) (Gibco # 10082-139) for 72 hours until reaching confluence. The cells were pre-incubated in media with compound and 0.2% DMSO (dimethyl sulfoxide) for 3 hours and then labeled by incubating in medium containing compound, 0.2% DMSO and 1 μCi/per mL of ^{14}C acetic acid for an additional 3 hours. After labeling, the cells were washed once with 1x PBS (Gibco #14190-144) then lysed overnight at 4°C in buffer containing 10% KOH and 78%(vol.) ethanol.

Cholesterol extraction and data analysis:

Lipid ester bonds were hydrolyzed by saponification of the lysates at 60°C for 2 hours. Sterols (including cholesterol) were extracted from saponified lysates by combining with 3 volumes of hexane and mixing by pipette 6 times. The upper organic phase solution was collected and combined with an equal volume of 1N KOH in 50% methanol and mixed by pipette 6 times. The upper organic phase was collected in a scintilant-coated plate (Wallac #1450-501) and hexanes removed by evaporation at room temperature for 3 hours. The amount of ^{14}C cholesterol was quantified by scintillation counting in a Trilux 1450 plate reader (Wallac). The IC_{50} values were calculated from % inhibitions relative to negative controls vs. compound concentration on Microsoft excel 2000 data analysis wizard using a sigmoid inhibition curve model with formula:

$$y = Bmax\ (1-(x^n/K^n+x^n)) + y2$$

Where K is the IC_{50} for the inhibition curve, X is inhibitor concentration, Y is the response being inhibited and Bmax+Y2 is the limiting response as X approaches zero. Compounds of the invention have a L6 IC_{50} value greater than about 0.5 nM. See, for example, the compounds of Example 1, which has an L6 IC_{50} of 227 nM, Example 7, which has an L6 IC_{50} of 4330 nM, and the first entry in Table I, which has an L6IC_{50} of 0.84 nM.

Preferred compounds of the invention exhibit a hepatocyte selectivity greater than about 1000 ((L6 IC_{50} / Rat hepatocyte IC_{50}) > 1000), and have a L6 IC_{50} value greater than about 1nM.